UNIVERSITY OF SUSSEX

Novel Routes To Kainoids

The Total Synthesis of (-)-α-Kainic Acid

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A Thesis Submitted for the Degree of
Doctor of Philosophy

School of Life Science,

Department of Chemistry,

2013

I hereby declare that this thesis has not been and will not be submitted, in whole or in part to another University for the award of any other degree.

Signature:_____

Dedicated to my parents, Pete and Crys,

Without, their unremitting love and support I could never have hoped to achieve so much.

"Make poverty history, cheaper drugs NOW!"

Frank Gallagher (Shameless Ch. 4)

"There is nothing like looking, if you want to find something. You certainly usually find something, if you look, but it is not always quite the something you were after."

J. R. R. Tolkien

CONTENTS

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ABBREVIATIONS

9-BBN	-9-borabicyclo[3.3.1]nonane
Å	-Angström
Ac	-acetyl
AIBN	-azobisisobutyronitrile
aq.	-aqueous
Bn	-benzyl
Boc	-*tert*-butoxycarbonyl
Bu	-butyl
CAN	-ceric ammonium nitrate
cat.	-catalytic
Cbz	-carbobenzyloxy
Cod	-cyclooctadiene
conc.	-concentration
Cy	-cyclohexyl
Dba	-dibenzylideneacetone
DEA	-*N*,*N*-diethylaniline
DEAD	-diethylazodicarboxylate
DET	-diethyl tartrate
DEPC	-diethylphosphoryl cyanide
DHP	-dihydropyran
DIBAL-H	-diisobutyl aluminium hydride
DIPT	-diisopropyl tartrate
DMAP	-4-(dimethylamino) pyridine
DMF	-dimethylformamide
DMSO	-dimethylsulfoxide
Dppe	-1,2-bis(diphenylphosphino)ethane
Dr	-diastereomeric ratio
EAA	-excitatory amino acid
EDDA	-ethylenediammonium diacetate
Ee	-enantiomeric excess
Eqv	-equivalents
Et	-ethyl
H	-hours

HMPA	-hexamethylphosphoramide
i	-*iso*
IR	-infrared
K	-kilo
L	-ligand
LAH	-lithium aluminium hydride
LDA	-lithium diisopropylamide
LG	-leaving group
LiHMDS	-lithium hexamethyldisilazide
Min	-minutes
M	-molar
Me	-methyl
Mes	-mesityl
Mol	-mole
MOM	-methoxymethyl
Mp	-melting point
MS	-molecular sieves
n	-*normal*
NMR	-nuclear magnetic resonance
Pf	-phenylfluorenyl
PG	-protecting group
Ph	-phenyl
PMB	-*para*-methoxybenzyl
PPO	-pyrophosphate
PPTS	-pyridinium *para*-toluene sulfonate
Pr	-propyl
PTSA	-*para*-toluenesulfonic acid
R	-unspecified group of atoms
RCM	-ring closing metathesis
ref.	-reference
R_f	-retention factor
Rt	-room temperature
S	-seconds
s	-*sec*
sat.	-saturated
SM	-starting material

t	-*tert*
TBAF	-tetrabutylammonium fluoride
TBDMS	-*tert*-butyldimethylsilyl
TBHP	-*tert*-butyl hydroperoxide
TBS	-*tert*-butyldimethylsilyl
Temp	-temperature
TES	-triethylsilyl
Tf	-trifluoromethanesulfonate (triflate)
THF	-tetrahydrofuran
THP	-tetrahydropyranyl
TIPS	-triisopropylsilyl
TLC	-thin layer chromatography
TMANO	-trimethylamine *N*-oxide
TMS	- trimethylsilyl
Tol	-toluyl
Tr	-trityl
Ts	-tosyl
UV	-ultraviolet

ABSTRACT

UNIVERSITY OF SUSSEX

STEPHEN PETER GARNETT RUSHTON

DOCTOR OF PHILOSOPHY

NOVEL ROUTES TO KAINOIDS:
THE TOTAL SYNTHESIS OF (-)-α-KAINIC ACID

This thesis contains three chapters concerning synthetic studies towards the alkaloids (-)-α-kainic acid; a natural product isolated from the Japanese marine algae Kainin-sou (海人草) or *Digenea simplex* and the close family member (-)-domoic acid isolated from another Japanese marine algae Doumoi or *Chondria armata*.

Chapter one gives an introduction to the isolation, structure and biological activity of kainic acid, domoic acid and their analogues. Chapter one also contains a discussion of the previous syntheses of both kainic acid, domoic acid and domoic acid C. It is written with the aim of selecting key aspects of each synthesis and in turn gives a critical account of each piece of work. Chapter two is concerned with the results obtained from the experimental section of this thesis. Disclosed is a novel method for the construction of (-)-α-kainic acid via an ene-reaction on a 1,6-diene intermediate. The synthesis comprises of eight linear steps from readily available D-serine and through the use of simple methodology forms the target compound kainic acid in a satisfactory overall yield of 20 %. This thesis also investigates the possibility of installing a variety of side chains to the biologically active kainoid core via a cross-metathesis reaction on an unsaturated carbon appendage. Chapter three contains the experimental procedures carried out for the synthesis of the compounds discussed in chapter two.

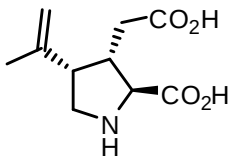
CHAPTER 1: Introduction

1.1 The Kainoid Amino Acid Family

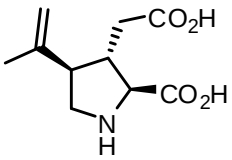
1.1.1 Background

The kainoid amino acids are an exclusive group of non-proteinogenic pyrrolidine dicarboxylic acids. They all have 3 asymmetric centres at positions 2, 3 and 4 of the pyrrolidine ring with the relative configurations; *S*, *S* and *S* or *R* respectively. Variations on the C-4 substituent where some degree of unsaturation is retained provide access to the different kainoids (**Figure 1.1**)[1].

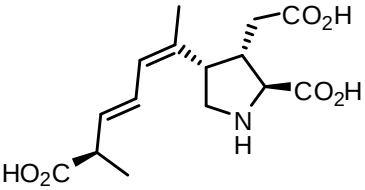
Kainoid amino acids are well known for their insecticidal and anthelmintic[2] properties. More importantly these excitatory amino acids (EAAs) are known for their neuroexcitatory activity in the mammalian central nervous system where they act as analogues of the excitatory amino acid L-glutamate (L-Glu)[3]. These biological properties have been well investigated with respect to neurodegenerative disorders such as Alzheimer's[4,5], Huntington's chorea[6,7] and epilepsy[8]. Today it is the interest in these properties that provides the driving force for these compounds as targets of asymmetric synthesis**.**



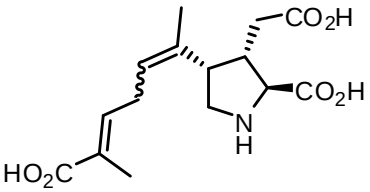
(-)-α-kainic acid (**1.1**)



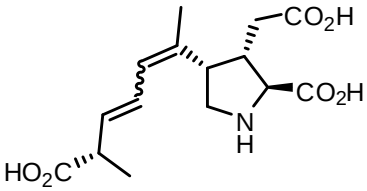
(+)-α-allokainic acid (**1.2**)



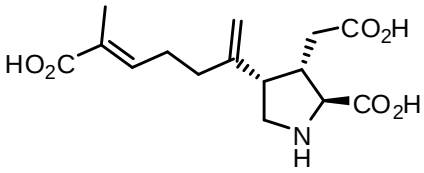
(-)-domoic acid (**1.3**)



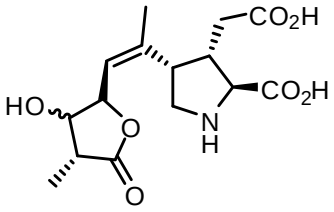
iso-domoic acid A (Z,E) (**1.4**)
iso-domoic acid B (E,E) (**1.5**)



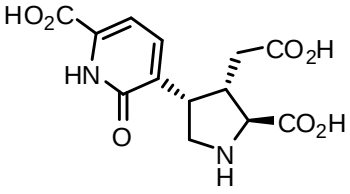
iso-domoic acid D (Z,Z) (**1.7**)
iso-domoic acid E (E,E) (**1.8**)
iso-domoic acid F (E,Z) (**1.9**)



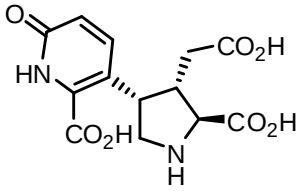
Iso-domoic acid C (**1.6**)



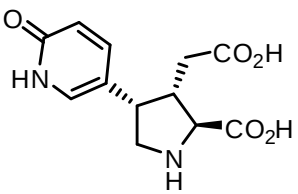
domoilactone A (4'S) (**1.10**)
domoilactone B (4'R) (**1.11**)



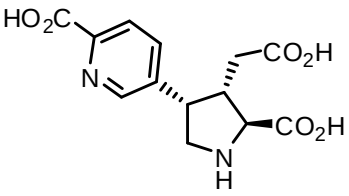
acromelic acid A (**1.12**)



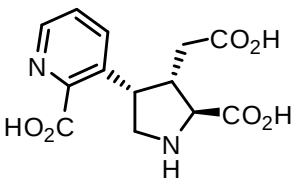
acromelic acid B (**1.13**)



acromelic acid C (**1.14**)



acromelic acid D (**1.15**)

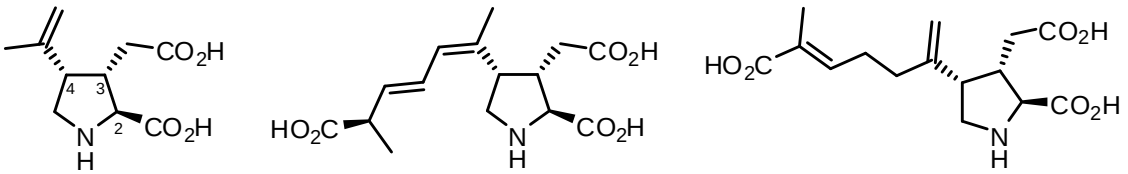


acromelic acid E (**1.16**)

Figure 1.1: Kainoid Amino Acids[1]

1.2 (-)-(α)-Kainic Acid (1.1), (-)-Domoic Acid (1.3) and Iso-domoic Acid C (1.6)

1.2.1 Background, Structure and Isolation



(**1.1**) (**1.3**) (**1.6**)

Figure 1.2: (-)-(α)-Kainic Acid (1.1), (-)-Domoic Acid (1.3) and Iso-Domoic Acid C (1.6)

The inhabitants of Japan have utilised the ability of kainoids to expel helminths or parasitic worms from the body for over a thousand years. Residents on Yakushima Island, just off the south eastern tip of mainland Japan, discovered that an extract of algae acted as a powerful insecticide[9]. The observation of these potent biological properties led to the first isolation of the parent member; (-)-α-kainic acid (**1.1**) or digenic acid, from extraction of the Japanese marine algae Kainin-sou (海人草) or *Digenea simplex* in 1953[10]. Kainic acid (**1.1**) has since been found in the algae *Centrocerus clavulatum*[11] and the Corsican moss *Alsidium helminthocorton*[12,13].

Structure elucidation *via* degradation studies carried out by Japanese groups in the 1950's[14-16], (a seminal example being soda-lime distillation which led to the isolation of a pyrrole) supported by X-ray experiments revealed the relative stereochemistry, however assignment of absolute stereochemistry remained elusive until Oppolzer and Thirring reported the total synthesis in 1982[17]. The carboxylate at the C-2 carbon and the alkyl carboxylate at the C-3 centre are each joined to the pyrrole ring through chiral carbons of *S* stereochemical configuration. In (-)-(α)-kainic acid the stereochemical configuration of the C-4 centre is also *S*. One example that demonstrates the importance of the stereochemistry in this molecule is an epimer of (-)-(α)-kainic acid which has an *R* configuration at the C-4 centre. This compound is called (+)-(α)-allokainic acid (**1.2**) (**Figure 1.1**) and has markedly reduced biological activity when compared to kainic acid(**1.1**)[18].

(-)-Domoic acid (**1.3**) contains an octadienic side chain at the C-4 carbon and was originally isolated from another Japanese marine algae Doumoi or *Chondria armata* in 1958[19]. Since then it has also been extracted from Canadian phytoplankton Pseudo-*nitzschia multiseries*

(formally *Nitzschia pungens f*)[20] and many other species of Pseudo-nitzschia following human poisoning from contaminated shellfish on Prince Edward Island in 1987[21]. The initially proposed *trans-trans* configuration of the alkene and unknown stereochemistry at C-5 carbon, were redefined as *cis-trans* with an absolute stereochemistry of *R* at the C-5 carbon following the total synthesis from Ohfune and Tomita also in 1982[22].

Iso-domoic acid C (**1.6**) is one isomer of many analogous to domoic acid (**1.3**). All of the iso-domoic acids contain the kainate core, can be isolated from both *Nitzschia pungens* and *Chondria armata* and exhibit insecticidal properties[9] although many including iso-domoic acid C (**1.6**) show markedly reduced activity when compared to domoic acid (**1.3**)[23,24].

1.2.2 Biological Activity

Kainates administered intravenously cause selective neuronal degeneration analogous to that seen in sufferers of Huntington's chorea[25]. Thus kainates have been used as tools in experimental models for Huntington's chorea[6,7] and other central nervous system disorders such as epilepsy[8], and senile dementia[26-29]. Due to their high neurotoxity in mammals, kainoids themselves are unlikely ever to become part of a treatment for such neuronal diseases. Despite this, the valuable information gained from experimental models has provided further identification of receptor subtypes and their distribution, which could lead to new solutions in the treatment of neuronal diseases for the future.

Kainates follow the same mode of action as L-Glutumate (L-Glu) after its release from glutamatergic nerve terminals. Both travel across the post-synaptic cleft to bind with their respective membrane bound receptors (GluRs)[30]. These EAA receptors are further sub-divided into the ionotropic receptors (iGluRs) which act as ligand-gated ion channels and regulate the movement of K^+, Na^+, and Ca^{2+} cations. Kainates act as agonists on the KA receptor subtype and on binding cause a confirmational change which allows an influx of cations into the post-synaptic cleft. These receptors play a key role in many fundamental processes including neuronal development, learning and memory, but cell death can occur due to overstimulation[30].

As with many of the kainoid amino acids' biological properties, the neuroexcitatory activity has been shown to be strongly dependent on the C-4 substituent[18,31,32]. CPAA (**1.17**), which has no C-4 appendage, shows no selectivity at kainate-type receptors (**Figure 1.3**)[31]. The orientation[18], π-nature[32] and conformation[31] of the C-4 substituent are all important factors in giving kainoids their excitatory activity. The *cis*-relationship existing between the C-3 and C-4 substituent's gives kainic acid (**1.1**) enhanced excitatory activity when compared to the C-4

epimer allokainic acid (**1.2**)[18]. π-Bond functionality has also been shown to be essential for neuroexcitatory activity[32]. Dihydrokainic acid (**1.18**), which has no π-electrons within its C-4 substituent, exhibits no excitatory activity (**Figure 1.3**) [31].

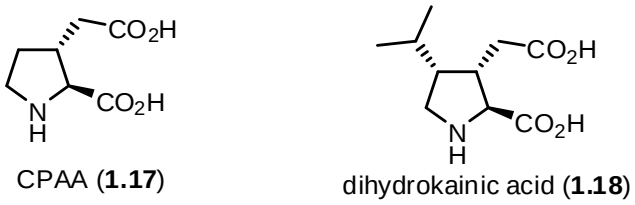
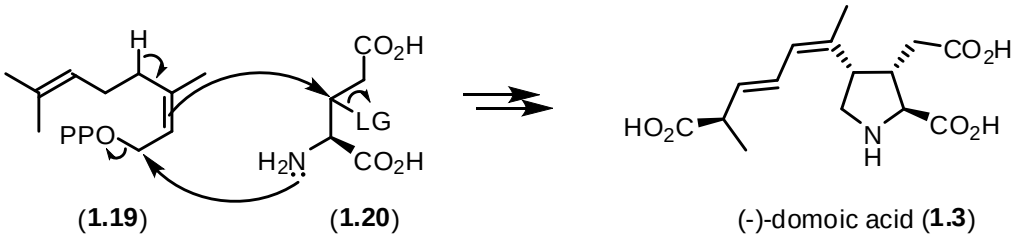


Figure 1.3: CPAA (1.17) and Dihydrokainic Acid (1.18)

1.2.3 Biosynthesis

An investigation into the biosynthesis of (-)-domoic acid (**1.3**) was undertaken by Wright *et al.*[33]. Labelling studies revealed evidence of condensation of a glutamic acid derivative (**1.20**) with a geranyl pyrophosphate (**1.19**) with subsequent cyclisation to form a proline ring (**Scheme 1.1**). A similar biosynthetic pathway was suggested for (-)-α-kainic acid (**1.1**) involving isopentenyl pyrophosphate instead of **(1.19)**. Separate experiments with [1-^{13}C]acetate and [1,2-^{13}C]acetate feedstocks and a *N. pungens* culture revealed a biosynthetic pathway whereby both biogenetic units are entirely derived from acetate[33]. Analysis of the labelling patterns from hyperfine splitting on ^{13}C-NMR spectra confirmed that the proline ring is derived from combination of a geranyl unit and an activated citric acid cycle intermediate. Further analysis of labelling patterns gave evidence that the geranyl portion of this molecule was of isoprenoid origin.



Scheme 1.1: Biosynthetic Pathway to Domoic Acid (1.3)

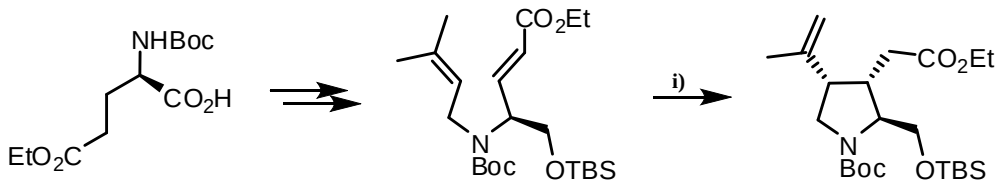
1.2.4 Previous Syntheses of (-)-(α)-Kainic Acid (1.1)

The non-trivial formation of the highly functionalised pyrrolidine ring containing three contiguous asymmetric centres has attracted significant synthetic interest, particularly with regard to the crucial *syn*-relationship that exists between the substituents at the C-3 and C-4

positions. Many past syntheses have solved this issue through a stereoselective formation of the C-3/C-4 bond or by controlling a stereoselective ring closure with the C-2 substituent. There have been more than 30 enantioselective syntheses and numerous racemic investigations covering a wide variety of strategies to the kainoid core (many of which are included in reviews by Parsons[1] and Moloney[30]). Despite this devotion placing kainic acid (**1.1**) as one of the most investigated synthetic targets to date. All syntheses are limited in yield, stereoselectivity and scale.

The following is by no means intended to provide a comprehensive review. The included examples have been chosen either as representatives of a particular synthetic approach, because they are relevant to this project or they have been completed within the last 5 years.

Oppolzer and Thirring described the first enantioselective synthesis of kainic acid (**1.1**) in 1982 (**Scheme 1.2**)[17]. Comprising of only six steps, this remains one of the simplest and shortest syntheses to date. The 1,6-diene intermediate (**1.22**) prepared from (*S*)-(+)-5-glutamate (**1.21**) was used stereoselectively to form the C-3/C-4 bond in kainic acid (**1.1**). This bond was formed by an intramolecular ene-reaction under the direction of the C-2 unit and afforded the pyrrolidine (**1.23**). Removal of the protecting groups and oxidation of the alcohol to the acid, gave kainic acid (**1.1**) in a respectable 5% overall yield.

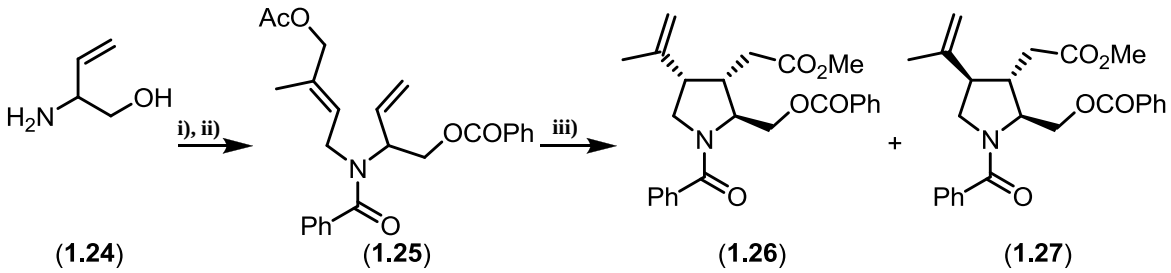


(**1.21**) (**1.22**) (**1.23**)

Reagents and Conditions: **i**. 5% solution in toluene, 130˚C, 40h (70%).

Scheme 1.2: Oppolzer and Thirring's Route[17]

The use of the ene-reaction to construct the kainoid skeleton was further developed by Yoo in 1990[34] (**Scheme 1.3**). Yoo utilised a palladium(0) catalysed formal ene-reaction or palladium(0) mediated olefin insertion-carbonylation reaction from a functionalised vinyl allylic acetate (**1.25**) to provide a mixture of the pyrrolidine ring systems found in kainoids (**1.26, 1.27**). The C-2 substituent controls the stereochemistry at C-3 but not C-4. It took an extra 5 steps to complete the synthesis of kainic acid (**1.1**).

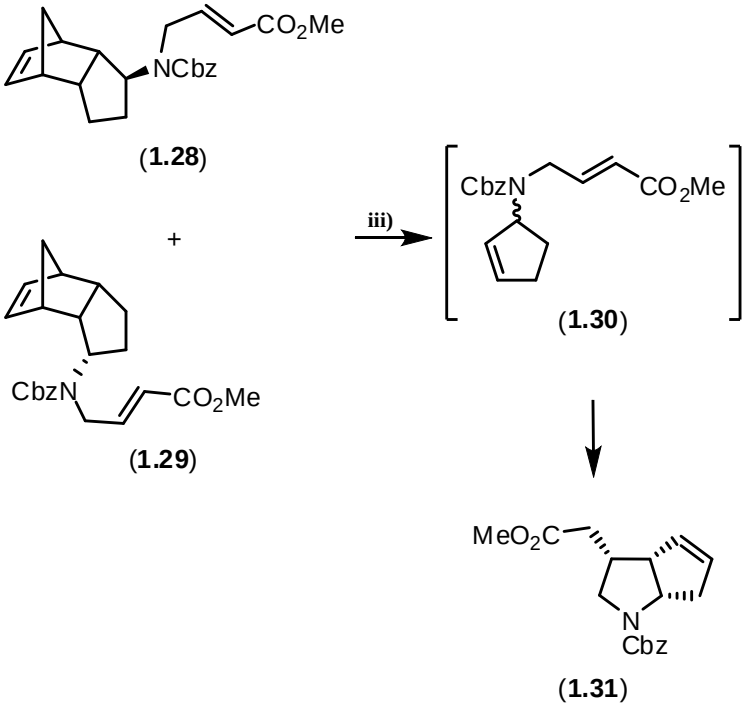


(**1.24**) (**1.25**) (**1.26**) (**1.27**)

Reagents and Conditions: **i**.  , **ii**. PhCOCl. **iii**. $Pd(dba)_2$ (7%), PPh_3 (15%), CO (3 atm), 80˚C in acetic acid followed by hydrolysis and esterification (25% and 35% respectively).

Scheme 1.3 Yoo's 1st Route[34]

Ogasawara's first synthesis of kainic acid (**1.1**) in 1997 also highlights the usefulness of intramolecular ene-reactions for construction of the kainoid core (**Scheme 1.4**)[35]. Precursors (**1.28 +1.29**) were formed from (±)-ketodicyclopentadiene and underwent a concurrent retro-Diels-Alder reaction and a synchronous, stereospecific ene-reaction of the transient 1,6-diene (**1.30**), to afford the all *cis*-product (**1.31**) in good yield and >99% ee. The bicyclic pyrrolidine **(1.31)** provided the skeletal structure to access kainic acid **(1.1**).

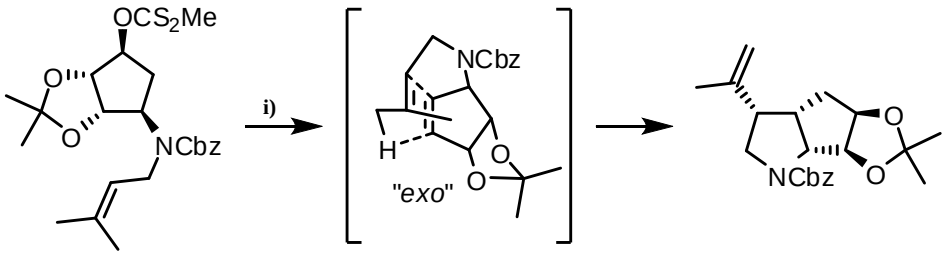


Reagents and Conditions: **i**. Ph_2O, reflux, (80%, >99ee).

Scheme 1.4: Ogasawara's 1st Route[35]

Ogasawara published a second synthesis of kainic acid (**1.1**) in 2000 involving a one-pot Chugaev *syn*-elimination and ene-reaction as the key step (**Scheme 1.5**)[36]. The xanthate ester (**1.32**) was obtained from enantiopure (+)-*cis*-4-carbobenzoxyamino-2-cyclopentenol.

Thermolysis of the xanthate (**1.32**) provided a single diastereomer of pyrrolidine (**1.34**). The authors suggest that the all *cis*-stereochemistry would be consistent with the formation of a transient *exo*-1,6-diene (**1.33**). Acid hydrolysis, cleavage and oxidation resulted in a diester, which underwent epimerisation of the C-2 position to give the correct configuration for (–)-kainic acid (**1.1**).

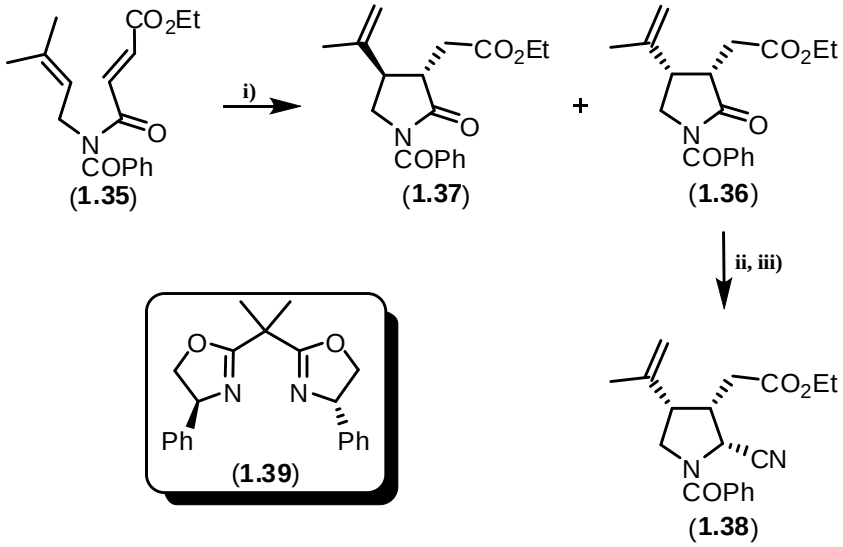


(**1.32**) (**1.33**) (**1.34**)

Reagents and Conditions: **i**. $NaHCO_3$, Ph_2O, reflux (72%).

Scheme 1.5: Ogasawara's 2nd Route[36]

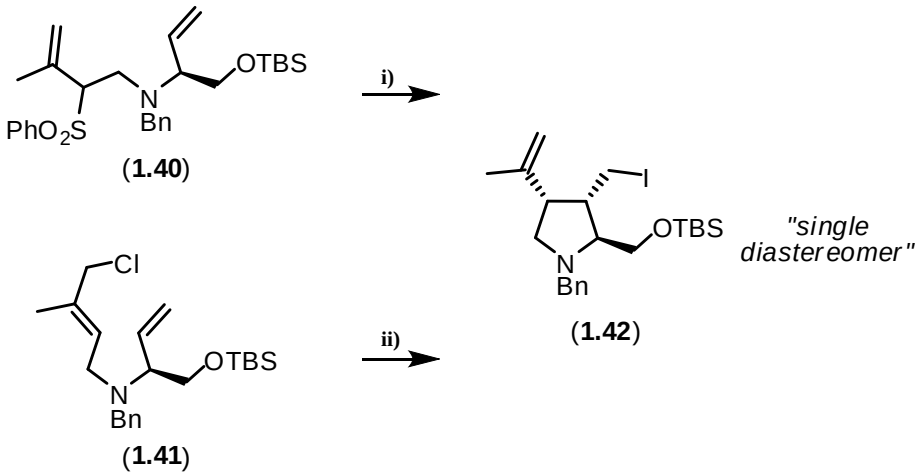
In 2000 Ganem utilised a metal-mediated enantioselective ene-reaction of the achiral diene (**1.35**) (**Scheme 1.6**)[37]. Bis-oxazoline ligand (**1.39**) directed high diastereoselectivity favouring pyrrolidine (**1.36**), however formation of the nitrile (**1.38**) failed to give the expected *trans*-selectivity. Further hydrolysis of both the ester and the nitrile groups, followed by base-promoted epimerisation of the C-2 substituent afforded (–)-kainic acid **(1.1)** in a good overall yield of 20%.



Reagents and Conditions: **i**. (**1.39**), $Mg(ClO_4)_2$, CH_2Cl_2 (72%, (**1.36**:**1.37**) (>20:1)); **ii**. Cp_2ZrHCl, THF. **iii**. TMSCN, CH_2Cl_2 (70% over 2 steps).

Scheme 1.6: Ganem's Route[37]

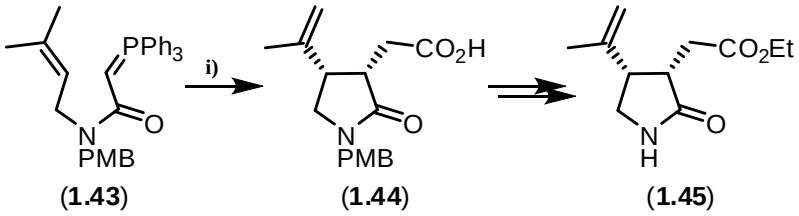
Chalker presented two, more syntheses in 2007[38] that highlight chemistry first pioneered by Oppolzer for creating *cis*-substituted heterocycles through the use of a palladium-catalysed zinc-ene cyclisation of allyl acetates[39]. Chalker applied this strategy to both an allyl phenyl sulfone (**1.40**) and allyl chloride (**1.41**) to provide the *cis*-substituted pyrrolidine precursor (**1.42**) that was readily converted to (–)-kainic acid (**1.1**) (**Scheme 1.7**).



Reagents and Conditions: **i**.1) $Pd^{(0)}$, $ZnEt_2$ 2) I_2 (55%); **ii**.1) $Pd^{(0)}$, $ZnEt_2$ 2) I_2 (91%).

Scheme 1.7: Chalker's Routes[38]

The most recent use of the ene-reaction has been in a neat synthesis from Tilve at the university of Goa in 2009 (**Scheme 1.8**)[40]. In this instance, he shows how a tandem Wittig-ene reaction can be used to install the desirable *cis*-C-3/C-4 stereocentres of kainic acid (**1.1**). Phosphorane (**1.43**) was prepared and upon refluxing with aqueous glyoxalic acid in toluene, pyrrolidone (**1.44**) was formed. This could then be deprotected and esterified in one reaction with ceric ammonium nitrate (CAN) and then re-esterifiied to Ganem's advanced intermediate (**1.45**)[37] without affecting the *cis*-stereochemistry.

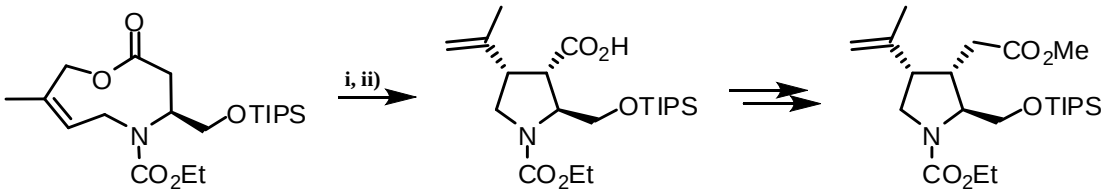


Reagents and Conditions: **i**. 50% aq. $CHOCO_2H$, toluene, 110°C, 24h, (60% (20:1 *cis*:*trans*)).

Scheme 1.8: Tilve's Route[40]

Knight communicated in 1987 that a stereocontrolled Ireland-Claisen rearrangement could be employed to construct kainic acid's (**1.1**) core structure (**Scheme 1.9**)[41,42]. Precursor

(**1.46**) was formed from L-aspartic acid and the enolate Claisen rearrangement gave exclusively the tri-substituted pyrrolidine (**1.47**) in a 55% yield following hydrolysis of the silyl ester. Arndt-Eistert homologation of the acid (**1.47**) gave the methyl ester (**1.48**), which was easily converted to kainic acid (**1.1**).

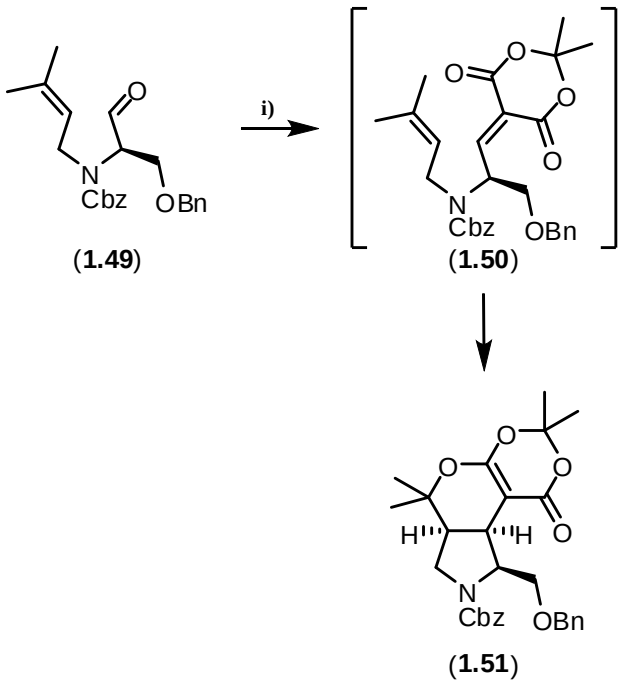


(**1.46**) (**1.47**) (**1.48**)

Reagents and Conditions: **i**. LDA, TBSCl, THF, -100 to 20ºC; **ii**. K_2CO_3, MeOH/H_2O (55% over 2 steps).

Scheme 1.9: Knight's Route[41]

In 1988 Takano uncovered an intramolecular Diels-Alder reaction of heterodiene (**1.50**) which, could be used to construct the *cis*-C-3/C-4 ring junction of kainic acid (**1.1**) (**Scheme 1.10**)[43]. The heterodiene (**1.50**), formed from a Knoevengal condensation of glyceraldehyde (**1.49**) with Meldrum's acid, participated in a spontaneous intramolecular [4+2]-cycloaddition to give (**1.51**) as a single diastereomer. The stereocontrol was theorised to be a result of the sp^2-planar-like configuration of the carbamate nitrogen, which allows efficient [4π+2π]-overlap of only the *endo*-conformer. The formation and subsequent opening of lactone (**1.51**) provided a suitable precursor to be taken on to kainic acid (**1.1**).

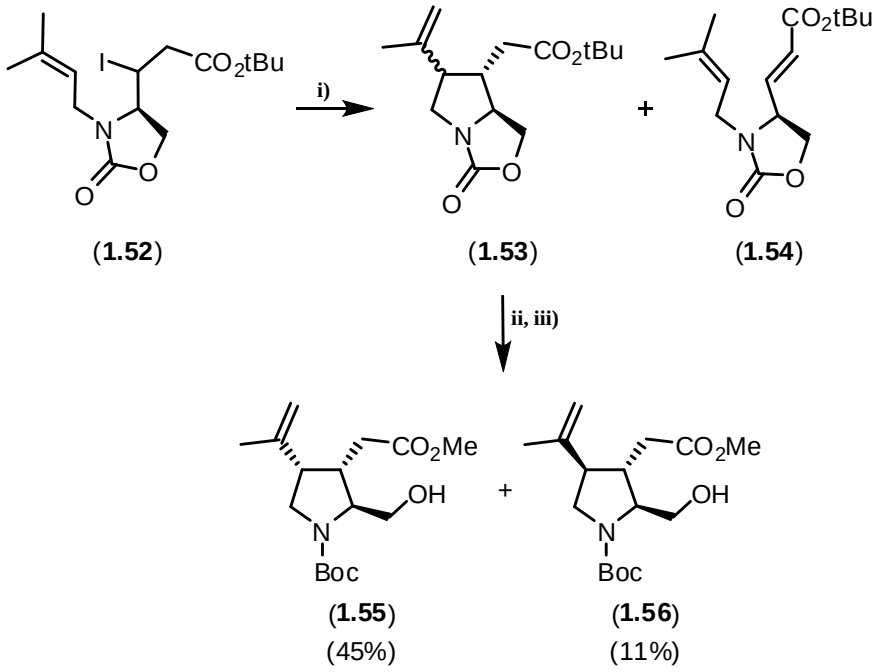


(**1.49**) (**1.50**) (**1.51**)

Reagents and Conditions: **i**. Meldrum's Acid, EDDA.

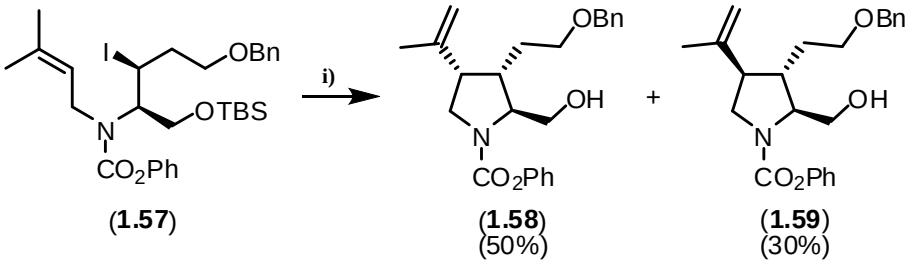
Scheme 1.10: Takano's Route[43]

In 1990 Baldwin showed the C-3/C-4 bond in kainic acid (**1.1**) could be constructed via a cobalt mediated radical cyclisation of an appropriately modified D-serine precursor (**1.52**) (**Scheme 1.11**)[44]. This method gave an inseparable mixture of the desired compound (**1.53**) and an α,β-unsaturated ester (**1.54**) Treatment with base, protection of the resultant amine and re-esterification, gave both C-4 isomers (**1.55** + **1.56**) in a 45% and 11% yield respectively. Baldwin observed that the constrained oxazolidinyl moiety enhanced C-3/C-4 stereocontrol during ring closure when compared to the previous approach involving the open chain iodide (**1.57**) (**Scheme 1.12**)[45,46]. The pyrrolidine (**1.55**) yielded kainic acid (**1.1**) in a further four steps.



Reagents and Conditions: **i**. $Co^{(I)}$, MeOH (51%, (**1.44**:**1.45**) (4:1)); **ii**. NaOH, dioxane, 70ºC then $(Boc)_2O$ **iii**. CH_2N_2, MeOH.

Scheme 1.11: Baldwin's 1st Route[44]

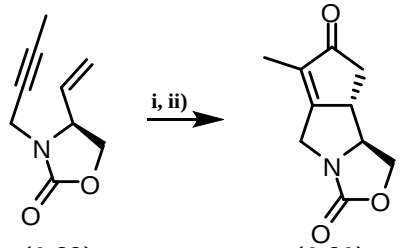


Reagents and Conditions: **i**. $Co^{(I)}$, MeOH.

Scheme 1.12: Baldwin's Open Chain Iodide Route[45,46]

In 1994 Yoo employed a rigid oxazolidinone moiety (**1.60**) in a Pauson-Khand reaction under standard conditions to provide exclusively the single diastereomer (**1.61**) in 93% yield

(**Scheme 1.13**)[47], thereby improving on his synthesis published a year earlier[48]. This again shows the usefulness of constraining the conformation of these molecules when seeking to install the *cis*-ring juncture of kainic acid (**1.1**). After further extensive manipulations involving formation of a lactone ring and subsequent reductive cleavage of the lactone, kainic acid (**1.1**) was finally obtained.

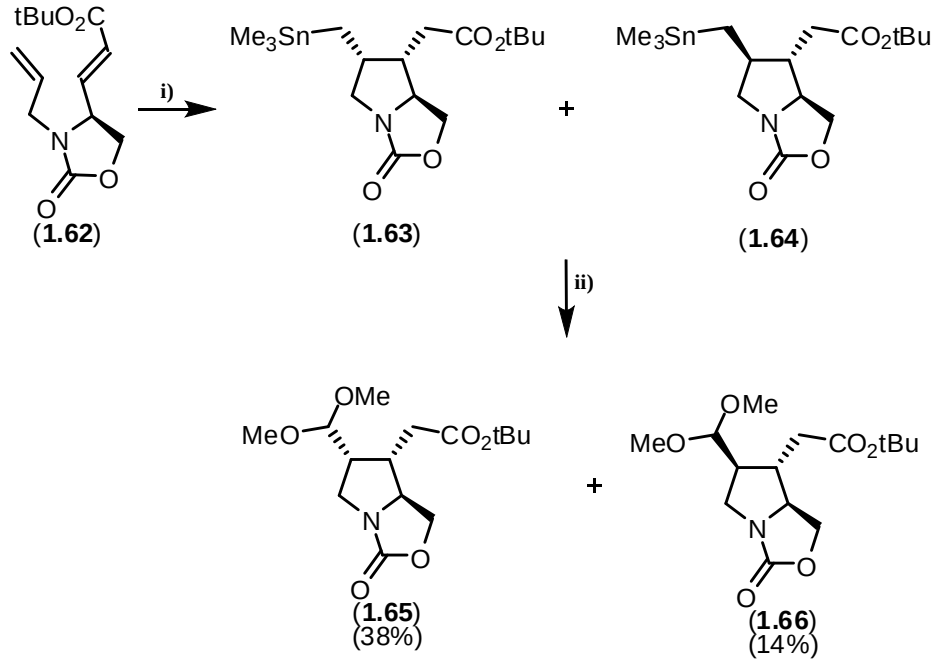


(**1.60**) (**1.61**)

Reagents and Conditions: **i**. $Co_2(CO)_8$, CH_2Cl_2. **ii**. TMANO (93% over 2 steps).

Scheme 1.13: Yoo's 3rd Route[47]

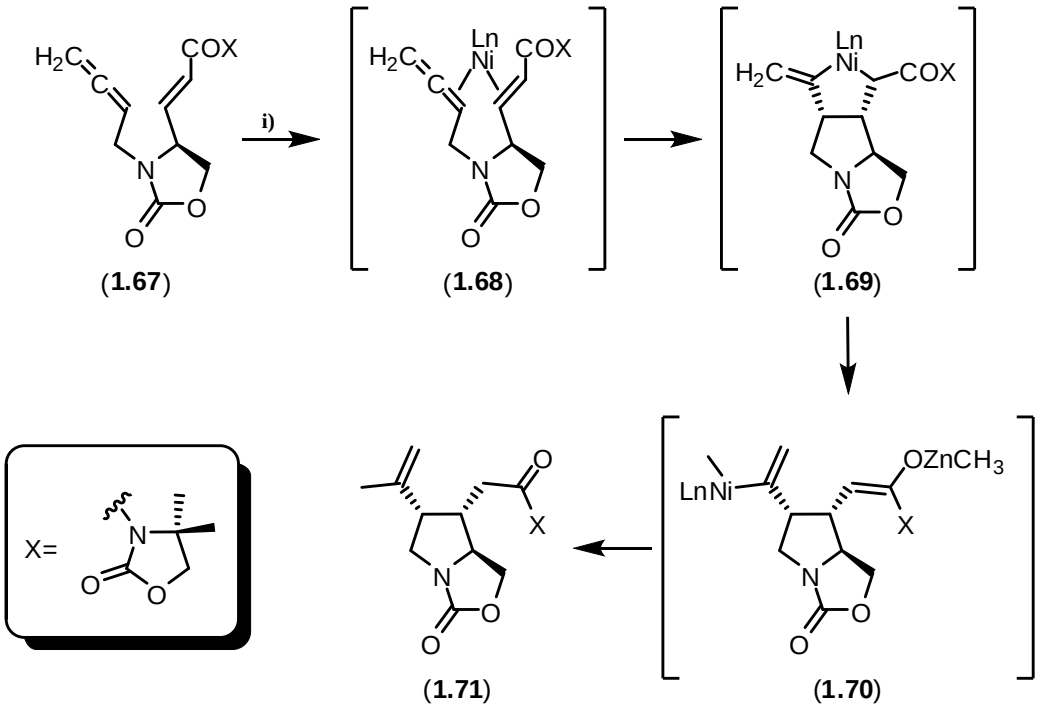
Hanessian published a synthesis of kainic acid (**1.1**) in 1996 which, proceeded via a trimethyl stannyl mediated radical carbocyclisation of an oxazolidinyl diene (**1.62**) (**Scheme 1.14**)[49]. This stereochemically controlled cyclisation provided predominately the bicycle (**1.63**), but also its inseparable C-4 epimer (**1.64**) in 88% yield and in a ratio of 2.8:1 respectively. The carbon-tin bond was then cleaved by CAN in methanol to give dimethyl acetals (**1.65** + **1.66**) in 36% and 14% yield respectively. Following careful elaboration to avoid any epimerisation of the C-4 centre, acetal (**1.65**) gave kainic acid (**1.1**).



Reagents and Conditions: **i**. Me_3SnCl, $NaCNBH_3$, ^tBuOH, AIBN, Δ (88%, (**1.63**:**1.64**) (2.8:1)); **ii**. CAN, MeOH, rt.

Scheme 1.14: Hanessian's Route[49]

In 1999 Montgomery highlighted a novel synthesis of kainic acid (**1.1**) which utilised a nickel mediated cyclisation of allene precursor (**1.67**) (**Scheme 1.15**)[50]. Interestingly the allene component of precursor (**1.67**) was installed following chemistry developed by Crabbé[51-53] for the homologation of an alkyne. Treatment of (**1.67**) with dimethylzinc in presence of biscod nickel and titanium isopropoxide directly afforded the bicyclic compound (**1.71**) in a reasonable yield of 57% and with a fortuitous diastereomeric ratio of 97:3 in favour of kainic acid's (**1.1**) stereochemistry.

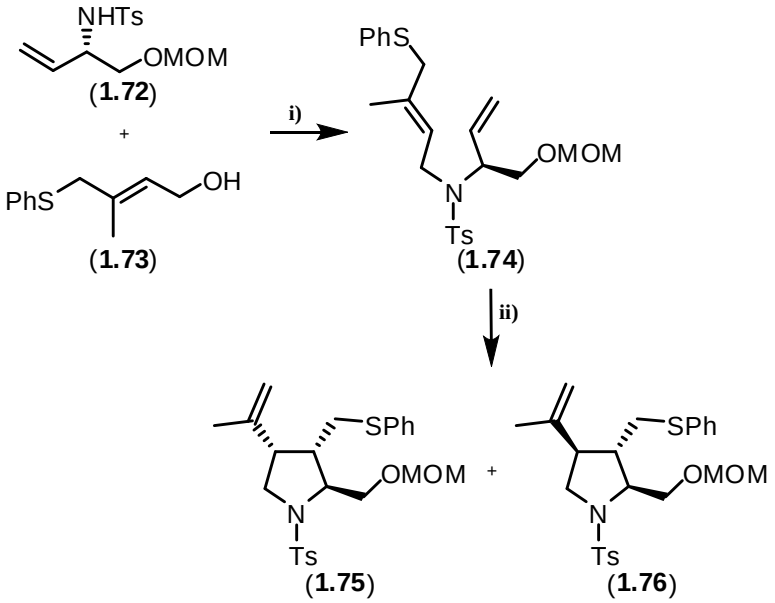


(**1.67**) (**1.68**) (**1.69**) (**1.70**) (**1.71**)

Reagents: **i**. MeLi/$ZnCl_2$, $Ni(cod)_2$ (10 mol %), $Ti(O\text{-}^iPr)_4$, (57% (97:3 diastereomeric ratio)).

Scheme 1.15: Montgomery's Nickel Catalysed Cyclisation[50]

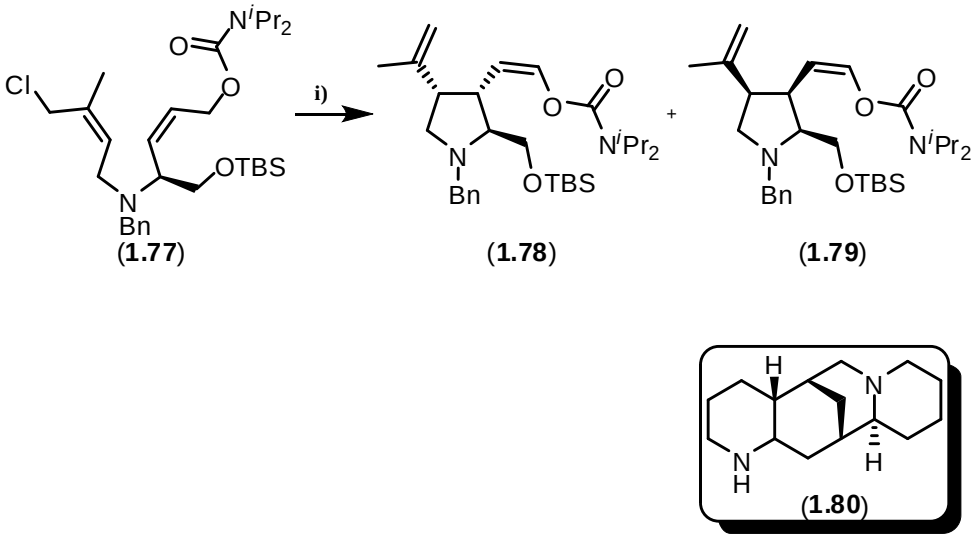
Naito's synthesis of kainic acid (**1.1**) in 2000 used sulphur chemistry to install the tri-substituted core (**Scheme 1.16**)[54]. Diene precursor (**1.74**) was built by combining (*S*)-vinylglycinol (**1.72**) with hydroxyl sulphide (**1.73**), and cyclised cleanly to give a mixture of C-4 isomers in a ratio of 2:3 in favour of (**1.75**). In this case it was shown that installation of an oxazolidinone ring actually impeded the cyclisation step leading to a recovery of starting material. Kainic acid (**1.1**) was obtained following a further seven steps.



Reagents and Conditions: **i**. PPh_3, DEAD, THF. **ii**. PhSH(cat.), AIBN, C_6H_6, Δ (95%, (**1.75**:**1.76**) (1:1.5)).

Scheme 1.16: Naito's Route[54]

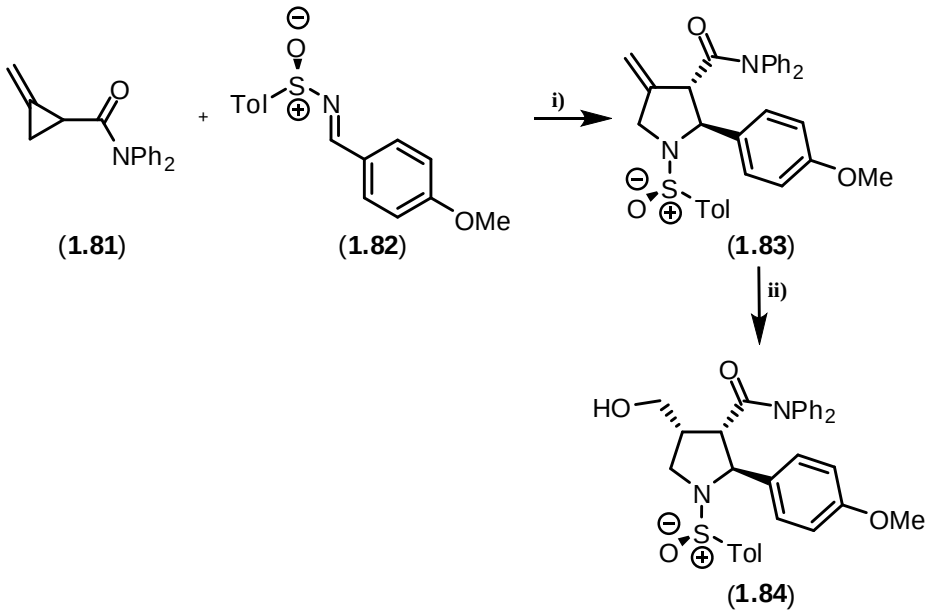
Hoppe achieved a diastereoselective total synthesis of kainic acid in 2004 (**1.1**) by using a (–)-sparteine (**1.80**) mediated asymmetric deprotonation of the carbamate (**1.77**), which then underwent a stereospecific intramolecular cyclisation to give the diastereomers (**1.78 + 1.79**) in a (8:2) ratio respectively (**Scheme 1.17**)[55]. He extended this work in 2005 to include an oxazolidinyl ring system, hoping to improve stereocontrol at the C-2 centre. Unfortunately as with Naito's work this too proved unsuccessful[56].



Reagents and Conditions: **i**. ^{n}BuLi, (**1.80**), toluene, -78°C (83%, (**1.78**:**1.79**) (8:2)).

Scheme 1.17: Hoppe's Route[55]

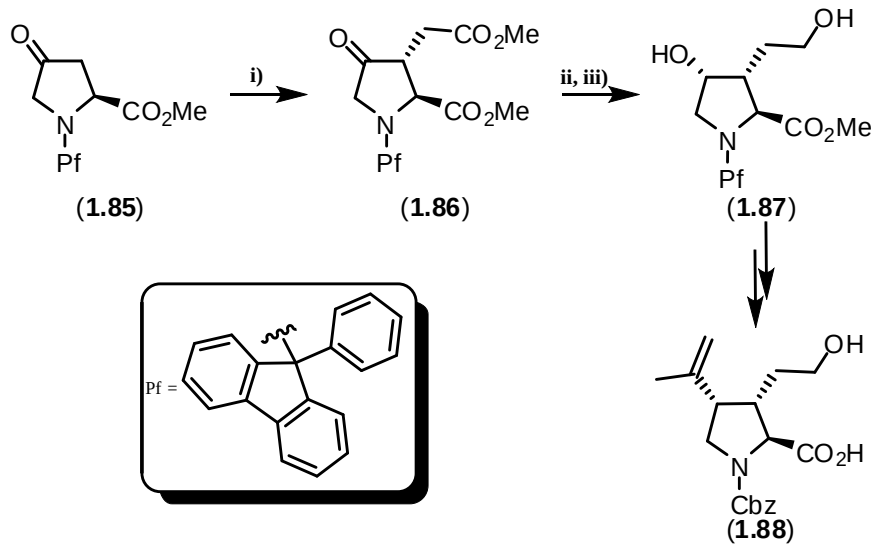
In 2005 Lautens reported an enantioselective synthesis of kainic acid (**1.1**) with an overall yield of 15%[57]. He utilised a MgI_2-mediated diastereoselective ring expansion of methylenecyclopropyl amide (**1.81**) in the presence of chiral sulphoxide (**1.82**) which, resulted in pyrrolidine (**1.83**) (**Scheme 1.18**). Kainic acids (**1.1**) remaining C-4 stereocentre was then incorporated after a diastereofacial hydroboration, followed by an oxidative work up to give the alcohol (**1.84**). It took a further laborious ten steps before kainic acid (**1.1**) was attained.



Reagents and Conditions: **i**. MgI_2, THF (78%); **ii**. 9-BBN, THF, 50°C then NaOH, H_2O_2 (91%).

Scheme 1.18: Lauten's Route[57]

Poisson's first stereoselective synthesis of kainic acid (**1.1**) came in 2005 and featured a diastereoselective enolate alkylation of ketone (**1.85**) to afford the intermediate (**1.86**). A chiral reduction gave the homo chiral diol (**1.87**) (**Scheme 1.19**)[58]. Further manipulation and displacement of the modified secondary alcohol, using an organocuprate procedure (developed by Anderson in a racemic synthesis of kainic acid (**1.1**)[59]), installed kainic acid's (**1.1**) C-4 isopropenyl group to give the kainic acid precursor (**1.88**).

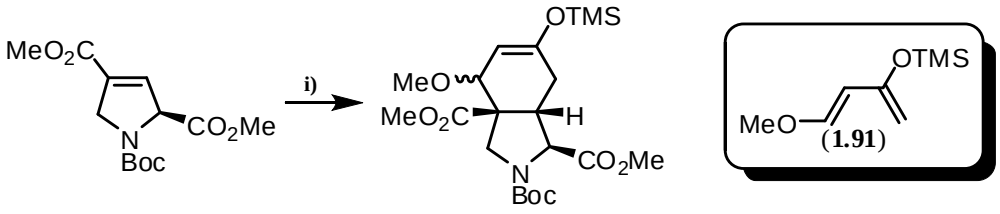


(**1.85**) (**1.86**) (**1.87**) (**1.88**)

Reagents and Conditions: **i**. ^{n}BuLi, HMPA, THF, -78 °C then $BrCH_2CO_2Me$, NaI, -40 °C (80% (dr 16:1)); **ii**. L-Selectride, THF, -78°C. **iii**. $NaBH_4$, EtOH, 0 °C (70% over 2 steps).

Scheme 1.19: Poisson's 1st Route[58]

Poisson presented a second synthesis of kainic acid (**1.1**) in 2006 (**Scheme 1.20**)[60]. A high pressure Diels-Alder reaction between Danishefsky's diene (**1.91**) and the vinylogous malonate (**1.89**) from a modified *trans*-4-hydroxy-L-proline resulted in the kainate precursor (**1.90**), in 80% yield and 90% ee. Further elaboration yielded kainic acid (**1.1**) in almost 10% overall yield. This approach has similarities with previous work by Ohfune and Tomita in their total synthesis of domoic acid (**1.3**)[22];

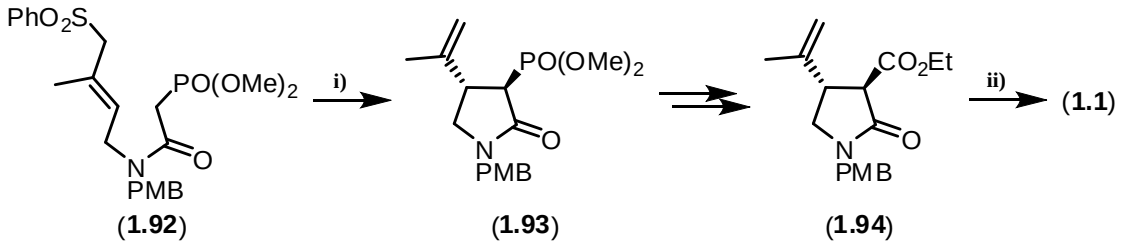


(**1.89**) (**1.90**)

Reagents and Conditions: **i**. (**1.91**), 20 °C, 15 Kbar, CH_2Cl_2 (80%, (90% ee)).

Scheme 1.20: Poisson's 2nd Route[60]

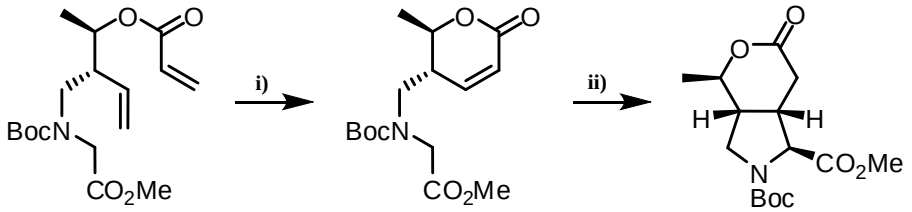
A formal synthesis by Madec and Poli in 2007 proceeded via an intramolecular palladium-catalysed allylic alkylation (**Scheme 1.21**)[61]. The cyclised pyrrolidone (**1.93**) was further functionalised through a Horner-Wadsworth-Emmons olefination, condensation with ethyl glyoxalate and subsequent reduction to intermediate (**1.94**), before following the same route as described by Ganem[37].



Reagents and Conditions: **i**. $[Pd(C_3H_5)Cl]_2$ (5 mol%), dppe (12.5 mol%), $^nBu_4NBr$ (10 mol%), KOH_{aq} (4 eqv), CH_2Cl_2-H_2O (1:1), rt, 16 h. (quantitative) *trans/cis* >95:5. **ii**. Ref. [37].

Scheme 1.21: Madec and Poli's Route[61]

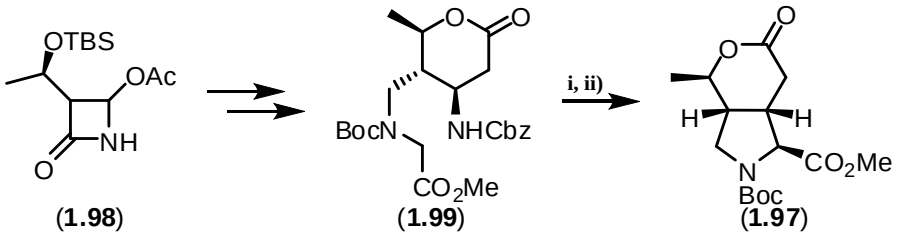
In 2007, Fukuyama demonstrated a total synthesis of kainic acid (**1.1**) whereby the trisubstituted pyrrolidine ring (**1.97**) was constructed using a ring-closing metathesis (RCM) upon an optically active acrylate (**1.95**) followed by an intramolecular Michael addition of the resultant α,β-unsaturated lactone (**1.96**) (**Scheme 1.22**)[62]. Both key reactions proceeded smoothly and further elaboration of bicyclic intermediate (**1.97**) yielded kainic acid (**1.1**) in 13% overall yield.



Reagents and Conditions: **i**. Hoveda-Grubbs' 2nd generation catalyst (0.8 mol%), $Cl_2(CH_2)_2Cl$, Δ, 3d. (99%). **ii**. LiHMDS, -60°C, (95% (C-2 epimer = 91:9)).

Scheme 1.22: Fukuyama's RCM Route[62]

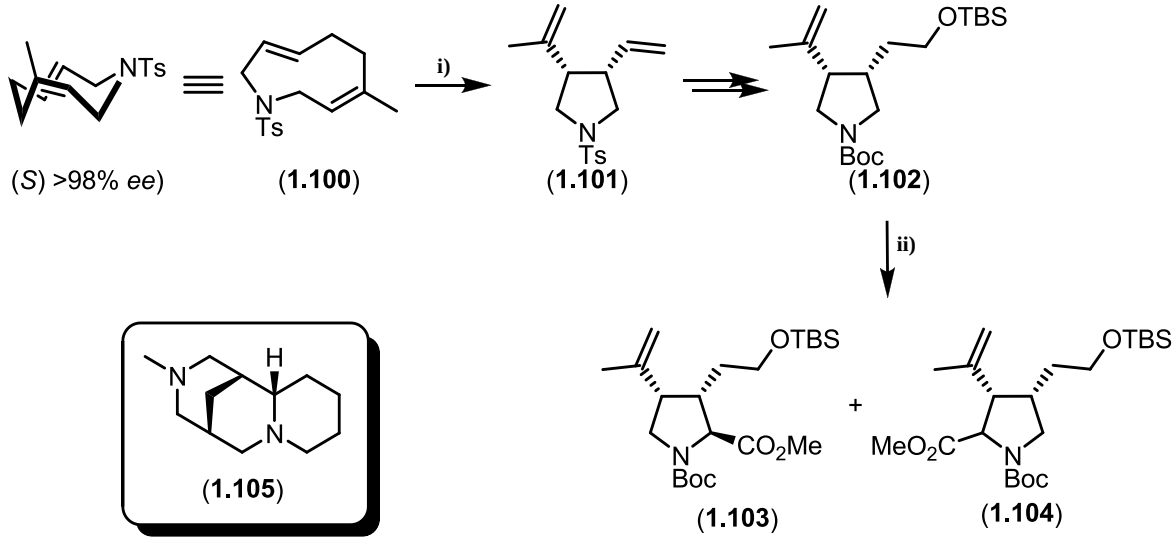
Fukuyama follows up this synthesis with a 2nd generation route in 2008, that proceeded via a one-pot sequential elimination-Michael addition of β-amino-δ-lactone (**1.99**) formed from an inexpensive azetidinone starting material (**1.98**) (**Scheme 1.23**)[63], whereby removing the need for an uneconomical RCM. The synthesis was completed in a similar fashion to his previous one in an overall yield of 14%.



Reagents and Conditions: **i**. LiHMDS (1eqv), CbzCl, DMF -60°C-rt, 20m. **ii**. LiHMDS (2.5eqv) -60°C. 20min. (94% (C-2 epimer 92:8)).

Scheme 1.23: Fukuyama's 2nd Generation Route[63]

Tomooka discovered an interesting route to kainic acid (**1.1**) in 2008 that proceeded through a palladium catalysed Cope rearrangement of chiral planar amide (**1.100**) to provide solely the desired product (**1.101**) in 94% yield and high diastereoselectivity (92:8) (**Scheme 1.24**)[64]. Selective hydroboration and an appropriate protecting group strategy gave access to intermediate (**1.102**) which, was converted into the desired C-2 carboxylation products (**1.103**) and (**1.104**) under control of external chiral ligand (**1.105**). Intermediate (**1.103**) could easily be separated from its diastereomer (**1.104**) through chromatography and derivatised to kainic acid (**1.1**).

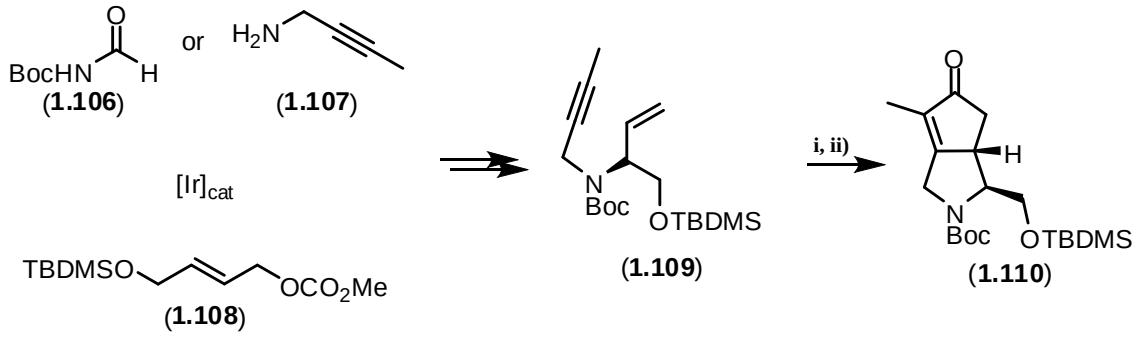


Reagents and Conditions: **i**. cat. $PdCl_2(PhCN)_2$, CH_2Cl_2, rt, (87% (>98% dr, >98% ee)). **ii**. ^{s}BuLi, (**1.105**) Et_2O, -78°C then $ClCO_2Me$, -78°C, (84% (**1.103**:**1.104** = 58:42)).

Scheme 1.24: Tomooka's Route[64]

Helmchen published a route in 2010 which uses an iridium catalysed allylic amination to construct the enyne precursor (**1.109**) required for an intramolecular Pauson-Khand reaction

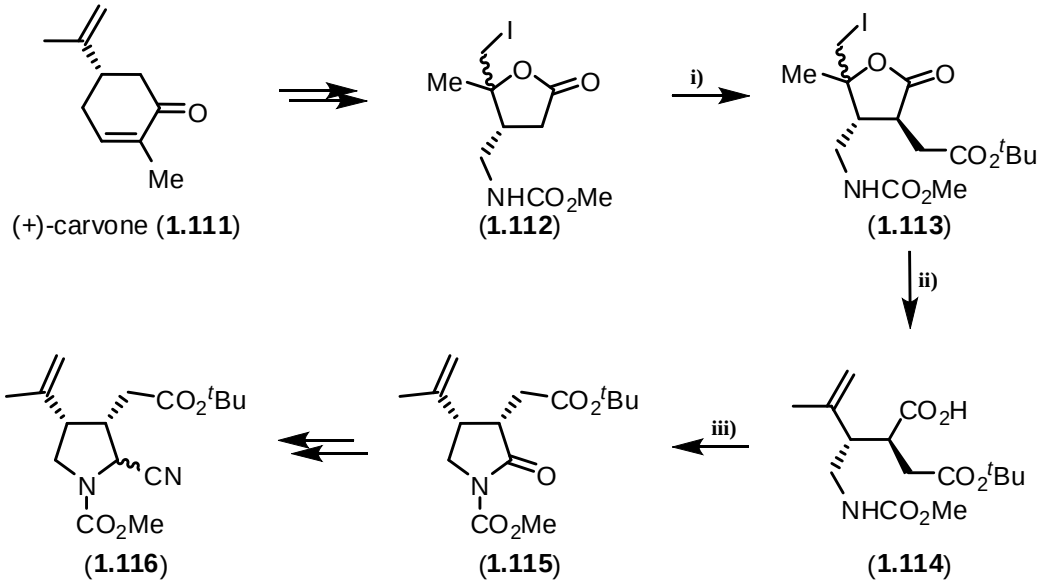
(**Scheme 1.25**)[65]. The cyclopentenone product (**1.110**) of this Pauson-Khand protocol was then elaborated to yield kainic acid (**1.1**) in an additional 6 steps.



Reagents and Conditions: **i**. $Co_2(CO)_8$, CH_2Cl_2, rt, 4h. **ii**. $Me_3NO.2H_2O$, 4Å MS, rt, 4h (57%).

Scheme 1.25 Helmchen's Route[65]

The most recent example to be found in the literature was published by Fukuyama *et al.*[66]. Starting from (+)-carvone (**1.111**), the route proceeds via the formation of a stable iodolactone (**1.112**) which rigidifies the molecule and allows for a stereoselective alkylation to introduce the C-3 unit (**Scheme 1.26**). A reductive ring opening facilitated by zinc in acetic acid followed by cyclisation provided the desired *cis*-substituted lactam (**1.115**) which, through a selective reduction and nitrile addition gave precursor (**1.116**). A base hydrolysis and concurrent epimerisation of the C-2 centre gave access to kainic acid (**1.1**) in a 10.3% overall yield from (+)-carvone[66].

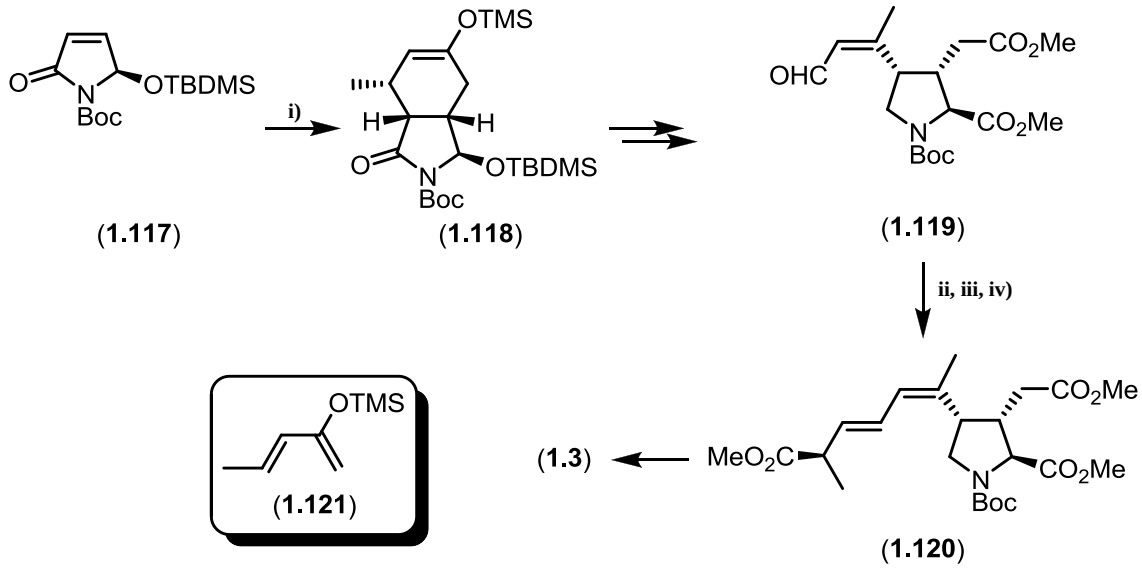


Reagents and Conditions: **i**. LiHMDS, THF, -78°C then $BrCH_2CO_2{}^tBu$ (82%), **ii**. Zn, AcOH, EtOH, 0°C-rt, **iii**. DEPC, Et_3N, CH_2Cl_2, rt (60% over 2 steps).

Scheme 1.26: Fukuyama's Synthesis[66]

1.2.5 Previous Syntheses of (-)-Domoic Acid (1.3) and (-)-Isodomoic Acid C (1.6)

Only one total synthesis of (-)-domoic acid has been reported; that of Ohfune and Tomita in 1982[22]. This approach uses Diels-Alder methodology to control the relative stereochemistries of both the C-3 and C-4 stereocentres by a [4+2] cycloaddition of unsaturated lactam (**1.117**) and siloxydiene (**1.121**) to yield bicyclic lactam (**1.118**) based on steric and electronic effects (**Scheme 1.27**)[22]. An oxidative cleavage of the cyclohexene ring in (**1.117**) was followed by a laborious sequence of functional group manipulations to provide (**1.119**). Use of an unstabilised ylid with predefined stereochemistry in a Wittig reaction gave the desired *E*-alkene. The primary alcohol was then oxidised and esterified providing a protected domoic acid (**1.120**) whereby saponification and acid treatment complete the synthesis of an optically pure (-)-domoic acid (**1.3**).



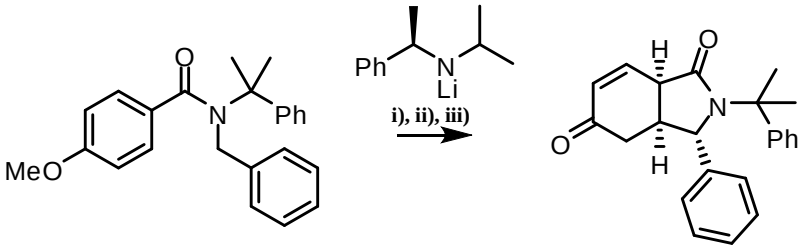
(**1.117**) (**1.118**) (**1.119**) (**1.121**) (**1.3**) (**1.120**)

Reagents and Conditions: **i**. (**1.121**), toluene, 135˚C. **ii**. ^{n}BuLi (2 eqv), , **iii**. Jones oxidation. iv.CH_2N_2.

Scheme 1.27: Ohfune and Tomita's Route[22]

In 2005 Clayden *et al*. published a synthesis of (-)-iso-domoic acid C (**1.6**)[67], which followed their previous work on kainoids[68,69]. An asymmetric deprotonation and cyclisation of an N-benzyl benzamide (**1.122**) followed by *in situ* hydrolysis provided bicycle (**1.123**). A recrystallisation from ethyl acetate was needed to achieve an enantiomeric enrichment of 99% however the yield associated with this transformation was a mere 38% overall. Eleven routine steps followed including the conjugate addition of a mixed cuprate, a sodium

periodate/ruthenium chloride oxidation and the oxidation of a selenide to complete this uneconomical synthesis with an overall yield of 0.4% in 15 steps.



(**1.22**) (**1.23**)

Reagents and Conditions: **i.** a: THF, -78 to 20˚C. b: HCl, H_2O, (62% (86% ee)). **ii.** Recrystallisation from AcOEt, (62% (99% ee)).

Scheme 1.27: Clayden's Route[67]

CHAPTER 2: Results and Discussion

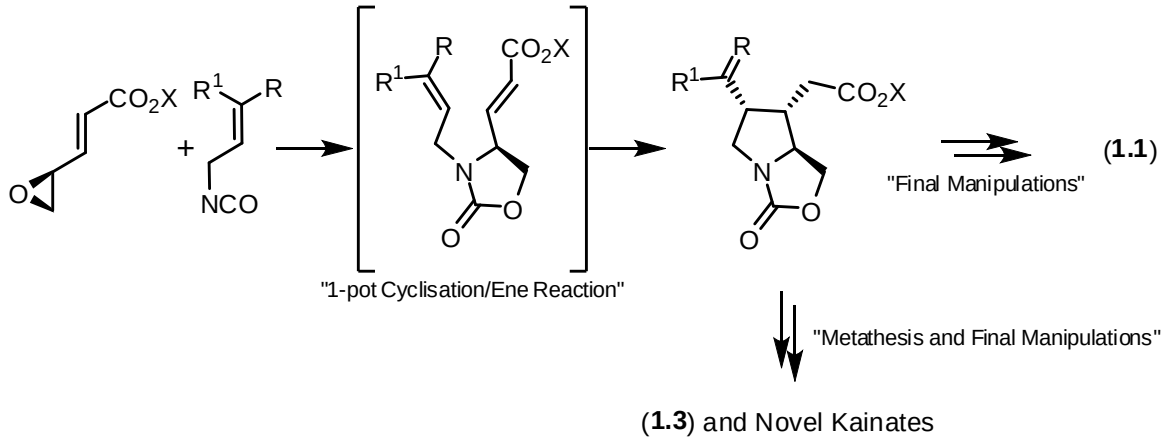
2.1 Project Aims

There is a very real need to develop a process for creating analogues of kainic acid (**1.1**) and domoic acid (**1.3**) in order to find novel antagonists that could play neuroprotective roles and alleviate or halt the progression of a variety of CNS disorders. This project aimed to develop an efficient synthesis of kainic acid (**1.1**) which would lead to a synthesis of domoic acid (**1.3**) and novel kainates. Hitherto the syntheses that have been published in the literature have encountered difficulties either giving rise to multi-step syntheses resulting in unacceptably low yields of the kainates or mixtures of isomers. Many laboratories over the world have produced syntheses that are much longer and less efficient than the original work of Oppolzer[17] and there is still a need to develop a highly efficient route to optically pure (-)-α-kainic acid (**1.1**) and other biologically important compounds containing the kainate motif.

Initially a 1-pot procedure to form the kainate ring system was planned. This involved the reaction of a suitably substituted isocyanate with an epoxide and then to extend this approach to other ring systems (**Scheme 2.1**).

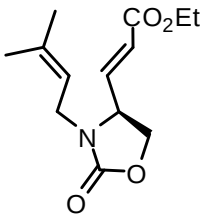
The following points formed a guideline for the project to adhere to:

- Use a short and novel approach to give a range of substituted kainates involving a simple condensation step.
- Proceed via an ene-reaction involving a substituted heterocyclic 1,6-diene to furnish kainate core in a stereoselective manner.
- Use the heterocyclic ring template to carry out a series of intermolecular metathesis reactions to furnish optically pure (-)-domoic acid (**1.3**) and other novel kainates (**Scheme 2.1**).
- Synthesis must be:
    - Economical (using cheap materials/reclaimable catalysts)
    - Efficient (high yielding chemistry)
    - Easily scalable
    - Avoid the use of toxic substrates where possible
    - Avoid use of toxic or heavy metals where possible
    - Use minimal chromatography
    - Avoid the use of protecting groups



Scheme 2.1: Initial Guidelines for Project

2.2 Chemistry of Ene-Precursor Oxazolidinone (2.1)



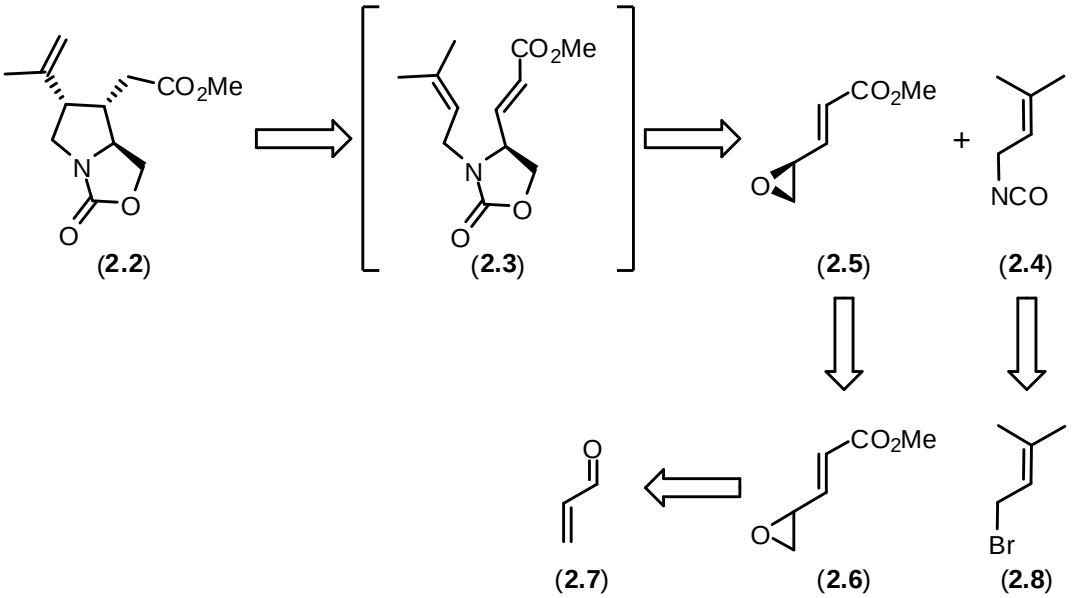
(**2.1**)

Figure 2.1: Ene-Precursor Oxazolidinone (2.1)

2.2.1 Route 1

2.2.1.1 Retrosynthetic Analysis 1

Retrosynthetic analysis of oxazolidinone (**2.2**) led to the hypothesis that the combination of allyl isocyanate (**2.4**) and epoxy allylic methyl ester (**2.5**) in a one-pot cyclisation/ene-reaction via the oxazolidinyl intermediate (**2.3**), would give ene-precursor (**2.2**) (**Scheme 2.2**). Oxazolidinone (**2.3**) is similar in structure to Oppolzer and Thirring's 1,6 diene (**1.22**) and could be used in the already well established ene-reaction route[17,34,35,37,40]. To generate the desired stereochemistry at the C-3 and C-4 positions in the natural product (**1.1**) the transition state for the ene-reaction should adopt the least sterically congested approach. Due to this steric crowding the *cis* hydrogens (shown in green) on the C-3/C-4 carbon atoms must both point up (**Figure 2.2**). 1-Bromo-3-methyl-2-butene (**2.8**) and acrolein (**2.7**) are both commercially available and through reported conditions can give access to the desired precursors of this synthesis[70-73].



Scheme 2.2: Retrosynthetic Analysis 1

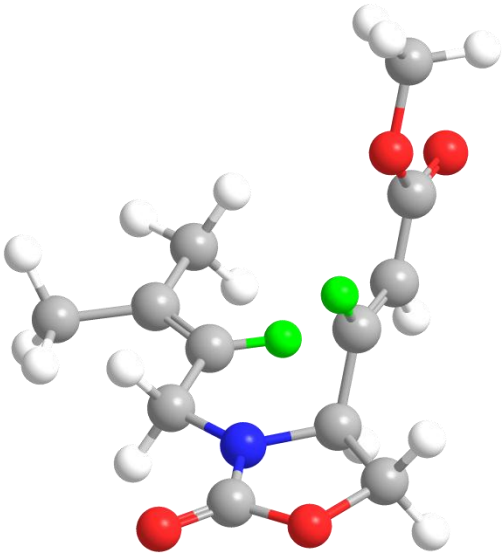
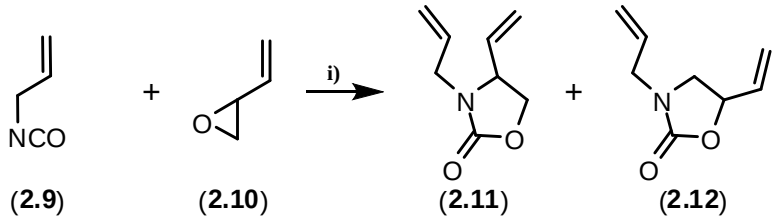


Figure 2.2: 3D Diagram of Ene-Precursor (2.3)

2.2.1.2 Model Studies

It has been known since 1958 that the reaction between isocyanates and 1,2-epoxides catalysed by a Lewis acid furnishes 2-oxazolidinones[74]. Combination of commercially available allyl isocyanate **(2.9)** with 1,3-epoxybutadiene **(2.10)** using a procedure developed by Herweh[75] formed an inseparable mixture of the desired 4-substituted 2-oxazolidinone **(2.11)** and undesired 5-substituted 2-oxazolidinone (**2.12**) in 60% yield and ratio of 1:3 respectively (**Scheme 2.3**).

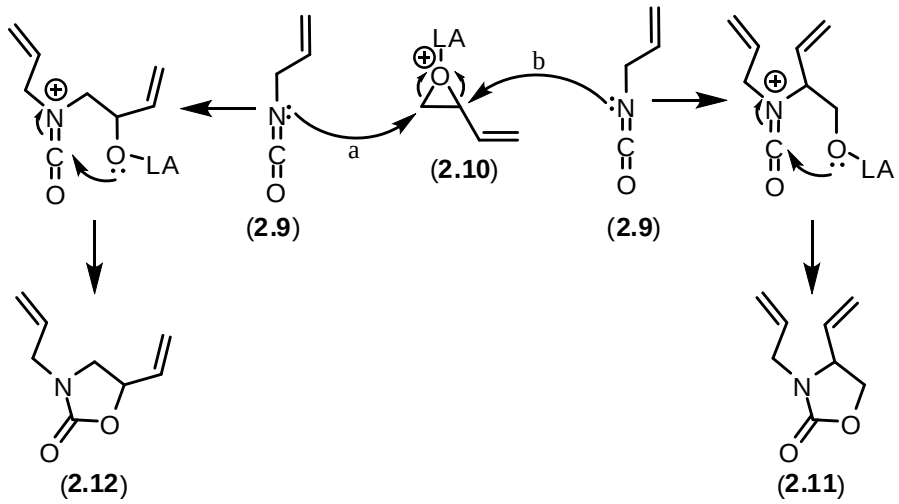


(**2.9**) (**2.10**) (**2.11**) (**2.12**)

Reagents and Conditions: **i**. DMF, LiCl, reflux 6h, (60% (**2.11**:**2.12** = 1:3)).

Scheme 2.3 Formation of Oxazolidinones (2.11) and (2.12)

A mechanism for the formation of oxazolidinones (**2.11**) and (**2.12**) was proposed (**Scheme 2.4**) whereby the epoxide (**2.10**) is activated by the lithium chloride Lewis acid allowing the lone pair on the isocyanate nitrogen (**2.9**) to attack at one of two positions on the oxirane ring (shown by arrows a and b). The electrophilic carbonyl carbon on the isocyanate is then attacked in *situ* by the lone pair of the oxiranyl oxygen to form the 4-substituted or 5-substituted oxazolidinone products (**2.11**) and (**2.12**). Both isomers were assigned by comparison of the ^{1}H-NMR spectra of the mixture of oxazolidinones (**2.11**) and (**2.12**) with known ^{1}H-NMR literature values for the 4-substituted oxazolidinone (**2.11**)[76]; no literature data was available for compound (**2.12**).



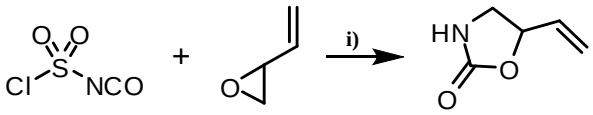
Scheme 2.4: Proposed Mechanism for Formation of (2.11) and (2.12)

Attempts to optimise the exclusive formation of model oxazolidinone (**2.11**) utilised a range of different solvents and catalysts, however none of the alternatives attempted revealed a more efficient process (**Table 2.1**). Similar isomeric ratios were seen by ^{1}H-NMR.

Entry	Solvent	Catalyst	Total Yield (2.11+2.12)
1	DMF	$CaCl_2$	NONE FOUND
2	THF	BF_3	NONE FOUND
3	THF	$Pd(PPh_3)_4$	NONE FOUND
4	MeCN	LiCl	NONE FOUND
5	DMSO	LiCl	18%
6	**DMF**	**LiCl**	**60%**

Table 2.1: Formation of Model Oxazolidinones (2.11 and 2.12)

When using the highly reactive chlorosulfonyl isocyanate (**2.13**)[77] it was possible to achieve oxazolidinone formation under vastly milder reaction conditions (**Scheme 2.5**). The reaction could advance in dichloromethane at room temperature without the need for a Lewis acid catalyst. The selectivity of this combination was however not advantageous and solely the undesired 5-substituted 2-oxazolidinone **(2.14**) was obtained in 51% yield. Investigation of this direction continued forward to prove whether the same selectivity would be seen in the real system.



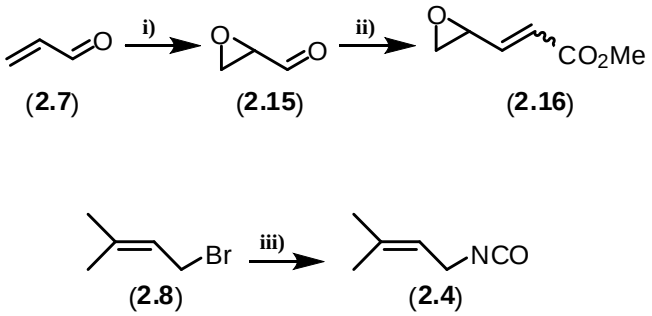
(**2.13**) (**2.10**) (**2.14**)

Reagents and Conditions: **i**.CH_2Cl_2, 0-25°C 6 h, then $KI_{aq,}$ 0°C, (51%).

Scheme 2.5: Formation of (2.14)

2.2.1.3 Precursor Synthesis

The chemistry employed to construct epoxide (**2.6**) is well established, starting with a base catalysed epoxidation of acrolein (**2.7**) (**Scheme 2.6**)[70]. A subsequent Wittig olefination[78,79] of the crude reaction mixture followed by vacuum distillation gave a 1:2 mixture of *cis*:*trans* geometric isomers in 46% yield. This method avoided the difficult isolation of glycidaldehyde (**2.15**)[71]. Isocyanate (**2.4**) was formed in 51% yield by combining commercially available 3,3-dimethylallyl bromide (**2.8**) and silver cyanate[72,73]. The volatility of isocyanate (**2.4**) under vacuum and polymerisation at higher temperatures yielded purification issues however, compound (**2.4**) was carried through to the next step while a new approach to avoid these problems was sought.



Reagents and Conditions: **i**. H_2O_2/H_2O, 1M NaOH, rt, **ii**. $(C_6H_5)_3P{=}CHCO_2CH_3$, MeOH 0°C-rt, overnight (46% from acrolein (*cis:trans* 1:2)), **iii**. AgOCN, diethyl ether, rt, overnight (51%).

Scheme 2.6: Formation of Precursors (2.16) and (2.4)

2.2.1.4 Attempted Formation of Racemic Oxazolidinone (2.17)

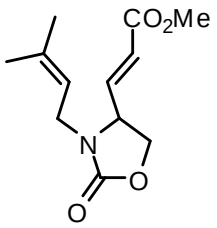
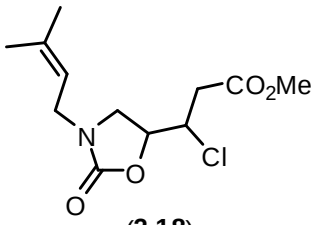


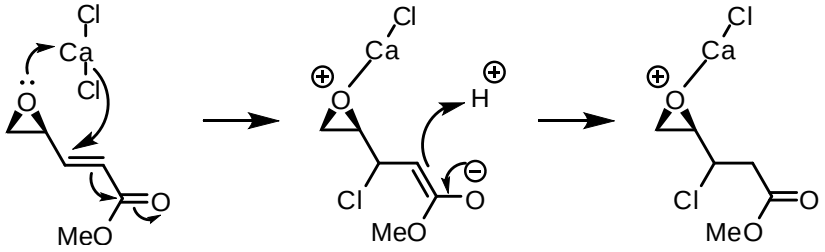
Figure 2.3: Oxazolidinone (2.17)

When the cycloaddition of precursors (**2.4**) and (**2.16**) was attempted, issues arose with the extraction of products on workup when using lithium chloride as a catalyst. This was thought to be caused by the presence of a partially water soluble urea formed from hydrolysed isocyanate[80] which caused the generation of a thick emulsion. Calcium chloride was used as an alternative and the reaction between epoxide (**2.16**) and isocyanate (**2.4**) progressed in an unsatisfactory 4% yield of new oxazolidinone (**2.18**); formed as one major diastereomer from ^{1}H-NMR evidence (**Figure 2.4**). The molecule had undergone a Michael addition of Cl^- (displaced from calcium chloride Lewis acid by the epoxide oxygen) to the α,β-unsaturated ester (**Scheme 2.7**). Examination of molecular models predicts the major diastereomer to have the chlorine atom pointing up in space. Due to the poor yield of chlorinated oxazolidinone (**2.18**) no further work was attempted on this molecule as it could not serve as a precursor to kainic acid (**1.1**) and hence the structure has not been confirmed.



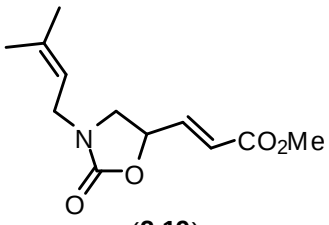
(**2.18**)

Figure 2.4: Chlorinated Oxazolidinone (2.18)



Scheme 2.7: Michael Addition of Chlorine Eliminated from Calcium Chloride

The next logical progression was to investigate the avenue of Lewis acid catalysts using triflate salts; in order to prevent the 1,4 nucleophilic addition of chlorine as discovered previously, increase yield and allow formation of our target ene-precursor (**2.17**). Scandium triflate failed to assist the cycloaddition and after 6 hours only starting material could be seen by TLC. Silver triflate was then tried in 10 mol%, under the standard reaction conditions, this unfortunately culminated in solely the undesired 5-substituted 2-oxazolidinone (**2.19**) being formed in a mere 17% yield (**Figure 2.5**). This highly unreliable reaction carried out in darkened glassware failed to provide a greater yield notwithstanding numerous changes to reaction protocol. It can also be noted that any attempts to scale up on the reaction from approximately 2 mmol scale (around 250 mg of **2.16**) saw a decrease in yield to *circa* 7%. The results are listed below (**Table 2.2**).



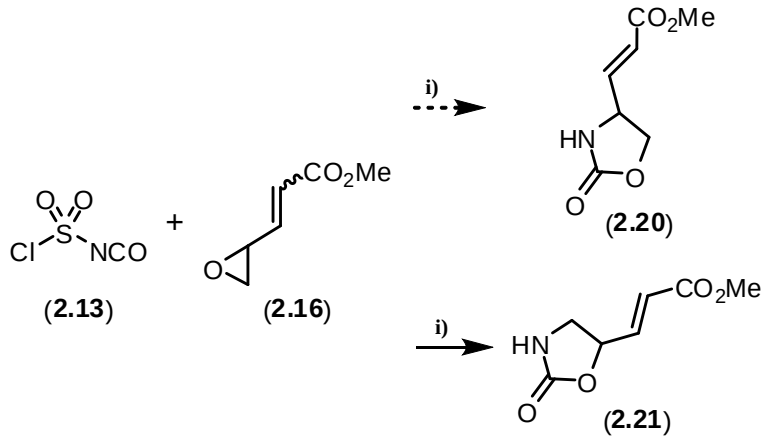
(**2.19**)

Figure 2.5: Undesired Oxazolidinone (2.19)

Entry	Reagents and Conditions	Catalyst	% Yield (2.19)
1	DMF, 1:1 (**2.16**:**2.4**)	ScOTf	No Reaction
2	**DMF, 1:1 (2.16:2.4)**	**AgOTf**	**17%**
3	DMF, 1:1.5 (**2.16**:**2.4**)	AgOTf	7%
4	DMF, 1.5:1 (**2.16**:**2.4**)	AgOTf	7%
5	CH_2Cl_2, 18 h reflux,	AgOTf	No Product found
6	1-methyl 2-pyrrolidinone	AgOTf	Decomposition of SM by TLC
7	DMSO	AgOTf	<5%
8	MeCN	AgOTf	No Reaction

Table 2.2: Formation of Oxazolidinone (2.19)

A change in route brought about by the aforementioned purity issues of isocyanate (**2.4**) and the lack of selectivity of the cycloaddition reaction when applied to the real system, planned to utilise an alkylation of the free NH on oxazolidinone (**2.20**) formed through the combination of chlorosulfonyl isocyanate (**2.13**) and epoxide (**2.16**) (**Scheme 2.8**). However, this had complications as not only did the reaction halt prematurely, but unsurprisingly the major products recovered were the undesired 5-oxazolidinone (**2.21**) and hydrolysed starting material. A variety of solvents and reaction temperatures were tested (**Table 2.3**) including the use of various equivalents of 1,2-epoxyhexane as an acid scavenger. To date the correct strategy has remained elusive and the highest yield of oxazolidinone (**2.21**) seen was 17%.



Reagents and Conditions: **i**. See **Table 2.3**

Scheme 2.8 Formation of Oxazolidinone (2.21)

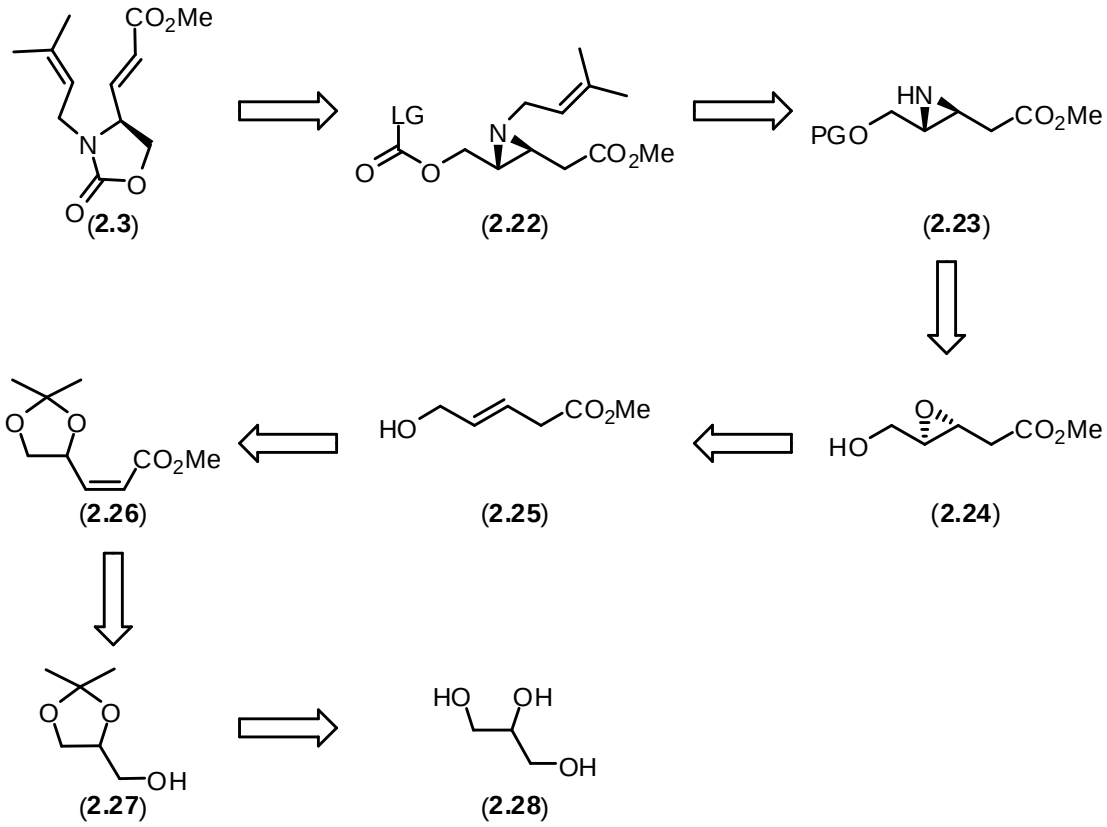
Entry	Reagents and conditions	% Yield (2.21)
1	**CH_2Cl_2, 0°C-rt, 4 h, sat. $KI_{(aq)}$**	**17%**
2	CH_2Cl_2, -10°C-rt, 4 h, sat. $KI_{(aq)}$	7%
3	CH_2Cl_2, -78°C-rt, 4 h, sat. $KI_{(aq)}$	15%
4	CH_2Cl_2, -10°C-rt, dihydrogen phosphate$_{(aq)}$	7%
5	Diethyl ether, -60°C-rt, 3 h	None Found
6	Nitromethane, -10°C-rt, 3 h	None Found
7	Toluene, -10°C-rt, 3 h	None Found
8	CH_2Cl_2, 60°C-rt, 3:4 (1,2-epoxyhexane : (**2.13**))	Mixed spot of (**2.21**) and cyclised epoxyhexane product
9	CH_2Cl_2, 60°C- rt, 3:1.05 (1,2-epoxyhexane : (**2.13**))	Mixed spot of (**2.21**) and cyclised epoxyhexane product
10	Neat	Addition halted as hazardous

Table 2.3: Formation of Oxazolidinone (2.21)

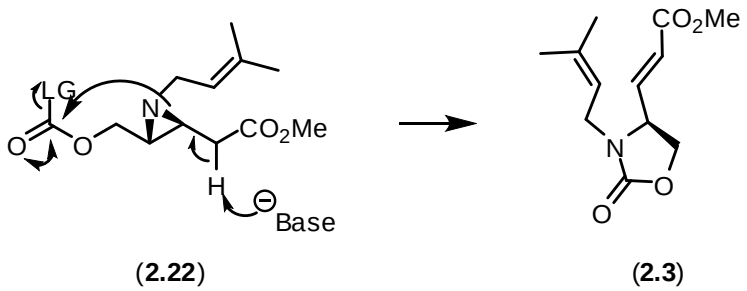
2.2.2 Route 2

2.2.2.1 Retrosynthetic Analysis 2

Due to continuing difficulties with expensive reagents leading to low yields of intermediates, it was illogical to move forward with the previous synthetic approach and a new route to the ene-precursor molecule (**2.3**) was devised. As shown in the retrosynthetic analysis (**Scheme 2.9**) it was hypothesised that the target precursor (**2.3**) could be constructed with the desired stereochemistry at the C-2 carbon from a base catalysed intramolecular cyclisation of chiral aziridine (**2.22**) (**Scheme 2.10**). It was envisaged that this intermediate would be accessible by alkylation of the aziridinyl nitrogen (**2.23**) constructed from a Staudinger reaction[81] on the asymmetric epoxide (**2.24**). Following the work as described by Pak and Lee, allylic alcohol (**2.25**) could be constructed in good yield through a reductive cleavage of alpha unsaturated ester (**2.26**) mediated by magnesium in methanol[82]. Sequential deprotection of ketal (**2.27**) then revealed glycerol (**2.28**) as a cheap alternative start material.



Scheme 2.9: Retrosynthetic Analysis 2



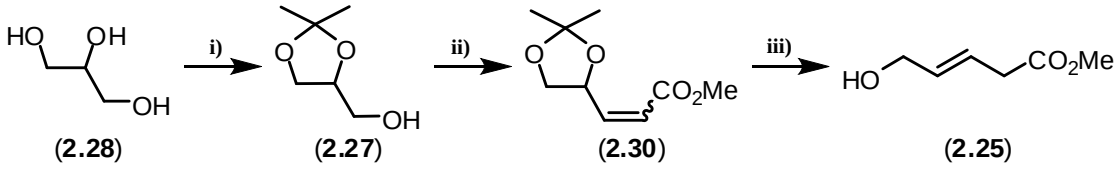
Scheme 2.10: Base Catalysed Cyclisation of Aziridine (2.22)

2.2.2.2 Chemistry of Aziridine (2.29)

(**2.29**)

Figure 2.6 Aziridine (2.29)

The first step of this new route involved a straightforward acid catalysed protection of glycerol (**2.28**) with acetone. Following an improved preparation of Fischer's original procedure[83] illustrated by Newman and Renoll in 1945[84] it was possible to make isopropylidene glycerol (**2.27**) in 95% yield (**Scheme 2.11**). Next a modification of Ireland and Norbecks one-pot Swern oxidation/Wittig procedure was used to convert the protected glycerol (**2.27**) into the desired allylic ester (**2.30**)[85]. This reaction proceeded smoothly on a multi-gram quantity scale to provide the unsaturated ester (**2.30**) as a mixture of *cis*/*trans*-isomers in a satisfactory 72% yield over the two steps and ratio of 10:77 respectively. These isomers are fully separable via column chromatography however, this is unnecessary for the next step. To furnish the necessary allylic alcohol (**2.25**) it was fitting to follow the reductive cleavage concept of using magnesium in methanol at -23 °C exposed by Pak *et al.* in 1993[82]. Following several unsuccessful attempts it was found that the addition of silicon carbide (carborundum) was necessary to activate the magnesium powder and initiate the radical production. This reaction gives as stated in the paper, solely the desired *trans*-alcohol due to the steric hindrance exerted by dioxanyl group on the conformation of the radical anion. This steric property must in turn control the stereochemistry of newly formed double bond[82]. The low yield of 64% this step has been attributed to the laborious task of purification due to the formation of extremely fine magnesium oxide which clogged any filtering media it came in contact with.



(**2.28**) (**2.27**) (**2.30**) (**2.25**)

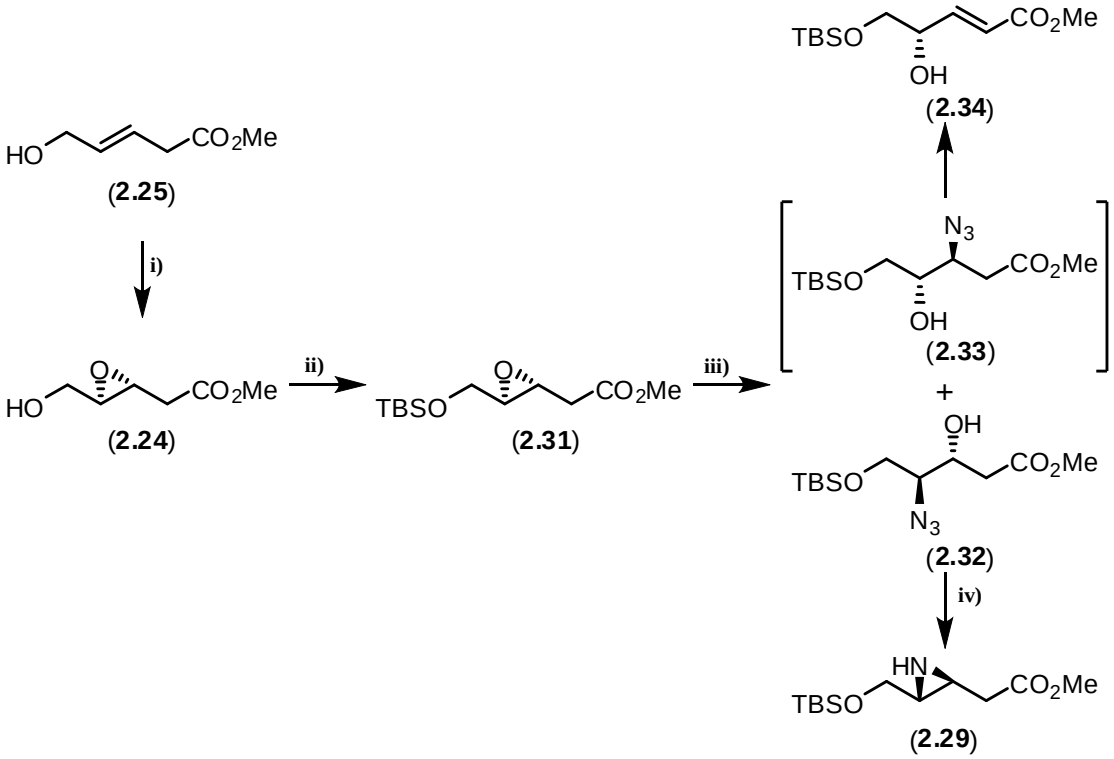
Reagents and Conditions: **i**. acetone, pentane, pTSA, Δ (temp @ head 31°C), 35 h (95%), **ii**. $(COCl)_2$, DMSO, Et_3N, $(C_6H_5)_3P{=}CHCO_2CH_3$, CH_2Cl_2, -78°C to -1°C, overnight (74% (*cis:trans* = 77:10)), **iii**. Mg, carborundum, MeOH, -23°C, 2 h (64%).

Scheme 2.11: Formation of Allylic Alcohol (2.25)

The enantioselective epoxidation of allyl alcohol (**2.25**), as according to the modified procedure developed by Sharpless proceeded extremely sluggishly at -20°C with (+)-diisopropyl L-tartrate and did not reach completion even after 31 days[86,87] (**Scheme 2.12**). Following a ferrous sulphate workup to destroy excess peroxide, the desired epoxy alcohol (**2.24**) was obtained using column chromatography on neutral silica in good yield (75%) based on recovered starting materials. The slow reaction rate is believed to have arisen due to coordination of the ligated titanium species to the additional oxygen functionality in the molecule. Epoxide formation would only have resulted when the titanium species coordinated to the appropriate alcohol functional group next to the double bond. With epoxy alcohol (**2.24**) in

hand the synthesis moved forward by protecting the alcohol group with a *tert*-butyldimethylsilyl moiety to provide silyl ether (**2.31**)[88].

The Staudinger protocol was next applied to construct aziridine (**2.29**) via hypothesised regioisomers (**2.32** + **2.33**)[81]. The first step was to combine epoxide (**2.31**) with sodium azide. Interestingly it was shown that in fact only formation of the azido alcohol (**2.32**) was possible as the azide group of the alternate organic azide (**2.33**) simply eliminated to form enone (**2.33**). The optimal method followed Zwanenburg and Nolte's protocol using ammonium sulphate as an additive and gave a return of 47% of useable intermediate (**2.32**) and 21% of enone (**2.34**)[89]. An analogous result was seen when using ammonium chloride however the overall yields were marginally less[90]. When using sodium azide not in combination with an ammonium salt solely the elimation product (**2.34**) was produced in a 51% yield[91]. The second part of Staudinger's protocol was to treat the organic azide with triphenylphosphine in acetonitrile and heat to reflux, producing the target aziridine (**2.29**) in an acceptable 79% yield. It must be noted that the enantiomeric enrichment calculations on the epoxy alcohol (**2.24**) were unfeasible using the standard Moshers ester method as under the reaction conditions molecular decomposition occurred.



Reagents and Conditions: **i**. $Ti(O^iPr)_4$, (+)-DIPT, TBHP, 4Å MS, CH_2Cl_2, -20°C, 31 Days, (75%), **ii**. TBSCl, imidazole, DMAP, CH_2Cl_2, 0°C, 1 h, (96%), **iii**. NaN_3, $(NH_4)_2SO_4$, MeOH/H_2O (v/v 10:3) (47% (**2.32**)), (21% (**2.34**)), **iv**. PPh_3, MeCN, Δ, 5h, (79%)

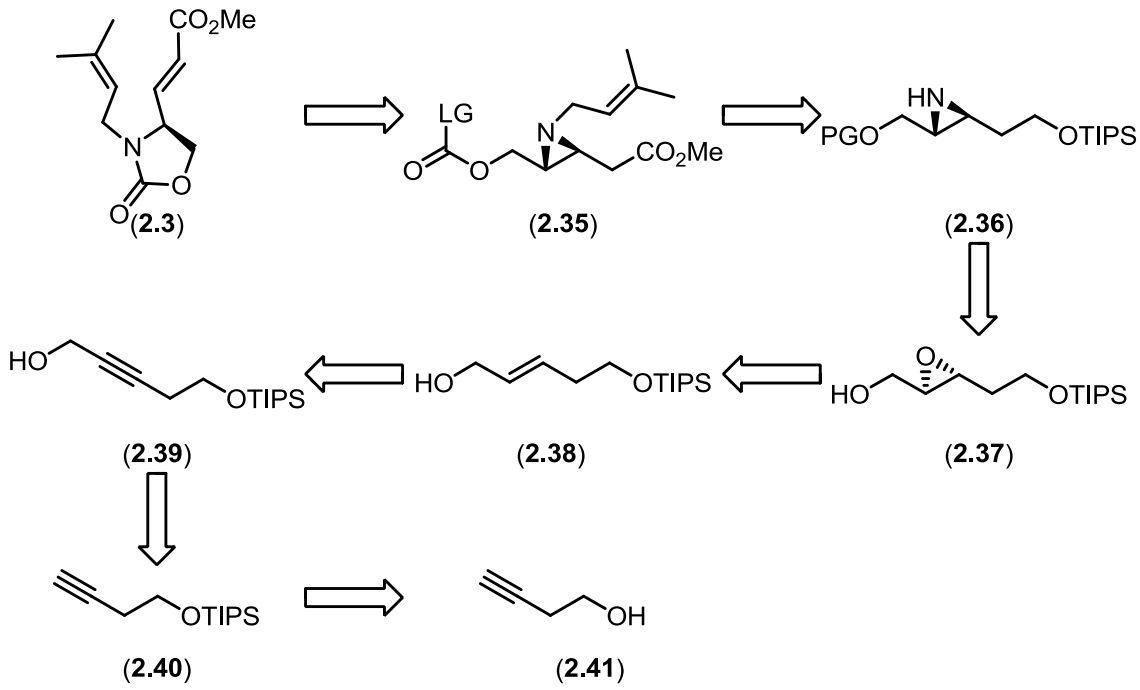
Scheme 2.12: Formation of Aziridine (2.29)

Deprotection of the silyl group on aziridinyl compound (**2.29**) was attempted regardless of the foreseen complications with any subsequent chemistry involving either, the carbonate formation from the revealed alcohol or possible alkylation of the nitrogen. Both of these steps were expected to be complicated due to labile acidic nature of the protons alpha to the carbonyl group. TBAF caused molecular destruction presumably, as stated by Corey, due to the sufficiently basic nature of F^- ion in tetrahydrofuran affecting a sensitive system[92]. In light of this, the removal of TBS protecting group was attempted with hydrofluoric acid. Under these conditions the reaction failed to yield any desired product.

2.2.3 Route 3: A Second Generation Route

2.2.3.1 Retrosynthetic Analysis 3

To circumvent the problem of the acidic nature of the α-protons due to the carbonyl functionality present in aziridine (**2.29**), the synthesis was modified by simply replacing the ester group with an alcohol. The retrosynthetic schematic delineates a route also employing Staudinger's method of aziridine formation (**Scheme 2.13**). Sequential disconnections from cyclisation precursor (**2.35**) exposed a protected diol (**2.36**). The free NH moiety of this molecule could be alkylated and, through use of an appropriate deprotection, carbonate formation and oxidation strategy, be manipulated to provide the target precursor (**2.35**). Moving linearly backwards through a Staudinger protocol on the enantiopure epoxide (**2.37**) formed from allylic alcohol (**2.38)** subsequent disconnections then revealed 3-butyn-1-ol (**2.41**) as an appropriate starting material for this synthesis.



Scheme 2.13: Retrosynthetic Analysis 3

2.2.3.2 Chemistry of Aziridine (2.42)

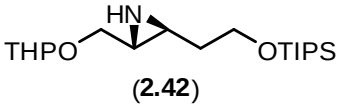
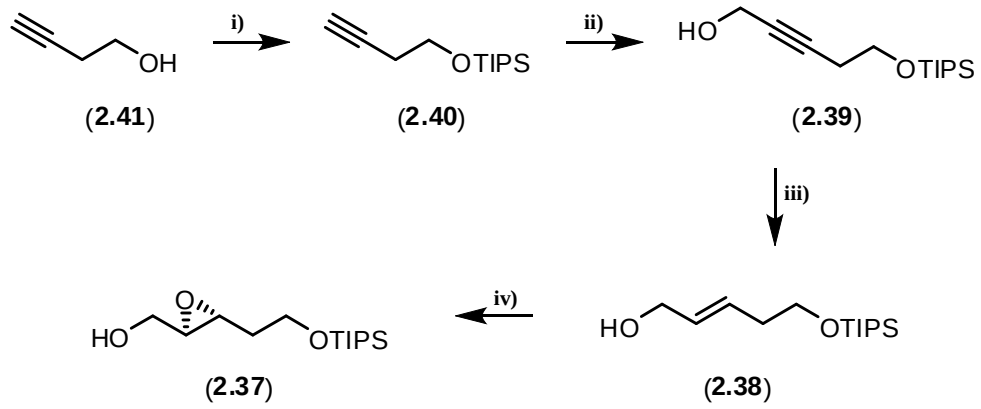


Figure 2.7: Aziridine Intermediate (2.42)

Following the work of Razon *et al*. the alcohol function of 3-butyn-1-ol (**2.41**) was protected as its triisopropylsilyl ether (**2.40**) in quantitative yield (**Scheme 2.14**)[93]. A high yielding homologation step followed and subsequent lithium aluminium hydride reduction of the resulting propargylic alcohol (**2.39**) constructed *trans*-allylic alcohol (**2.38**) in 98% yield[93]. A facile Sharpless asymmetric epoxidation utilising (+)-diisopropyl L-tartrate[87] gave the novel epoxy alcohol (**2.37**) in 67% yield and an enantiomeric excess of 64%. When using (+)-diethyl L-tartrate the reaction timing increased to around eight days. The yield associated with this epoxidation also increased to 76% however the enantiomeric excess of this epoxide fell to 22% ee. To determine and compare the enantiomeric excesses of the epoxides (**2.37**) resulting from the reaction of alkene (**2.38**) with DIPT and DET the Moshers esters of the epoxide mixtures from each reaction were synthesised following the work of Sharpless[94]. ^{1}H-NMR analysis focused on the terminal methylene protons of the primary epoxy alcohols. These protons were

observed as a diastereomeric pair of doublets of doublets (dd) around δ 4.65 (see appendices for ^{1}H-NMR spectra). The downfield pair was compared by integration to determine the enantiomeric excess. A racemic mixture was not prepared and the ^{19}F-NMR gave inconclusive data.



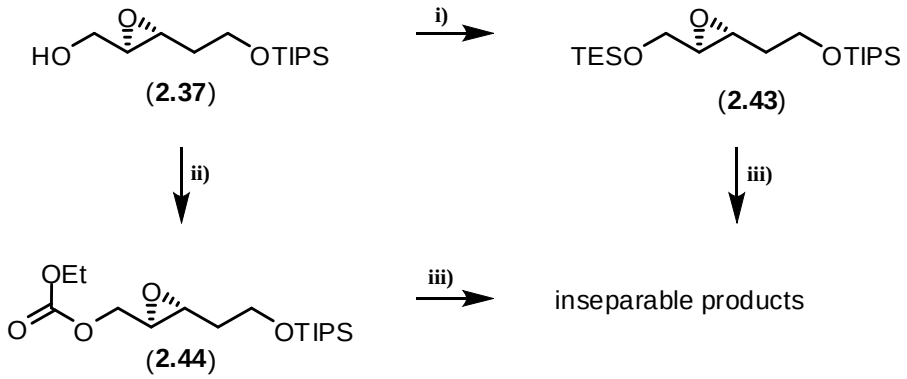
(**2.41**) (**2.40**) (**2.39**) (**2.38**) (**2.37**)

Reagents and Conditions: **i**. TIPSOTf, Et_3N, CH_2Cl_2, 0°C, 16 h (>99%), **ii**. ^{n}BuLi, paraformaldehyde, THF, -78°C, 6 h (92%), **iii**. LAH, THF, -10°C, 16 h (98%), **iv**. $Ti(O^{i}Pr)_4$, (+)-DIPT, TBHP, 4Å MS, CH_2Cl_2, -20°C, 16 h (67% and 82%ee).

Scheme 2.14: Formation of Epoxy Alcohol (2.37)

Two protecting group strategies were initially explored with respect to the free alcohol function of epoxide (**2.37**). It was postulated that an acid labile triethylsilyl protecting group would allow for easy removal following the aziridine formation. It was also pertinent to apply a carbonate group to this end of the molecule in the hope that it may remove the need for further deprotection steps later in the synthesis. $RuCl_3/NaIO_4$ should be sufficiently mild enough to oxidise the primary alcohol in presence of both the TES moiety and carbonate functionality[95]. The silyl protection of (**2.37**) with TES chloride progressed in 97% yield to give di-protected diol (**2.43**)[92] and the carbonate formation by combination with ethyl chloroformate gave a 95% return of carbonate (**2.44**)[96] (**Scheme 2.15**). On investigation both starting materials (**2.43**) and (**2.44**) gave complex inseparable mixtures of compounds under the standard Staudinger reaction conditions. Column chromatography was used to remove the major polar and non polar impurities; closer inspection of the ^{1}H-NMR spectra of the mixture of products revealed that the major product had both of these groups displaced by the azide anion. This was surprising in the case of the carbonate group which should have been stable to attack from such a nucleophile[95]. However, less so for the TES group which shares many similarities in reactivity with the trimethyl analogue[95]. Simultaneous opening of both epoxides was also seen in sparing quantities. This deduction is based on shifts in upfield CH_2 peaks representative of the changes in environment to protons situated within appropriate distances of the epoxide ring and confirmed by the infrared spectrum which showed the presence of both azide and alcohol

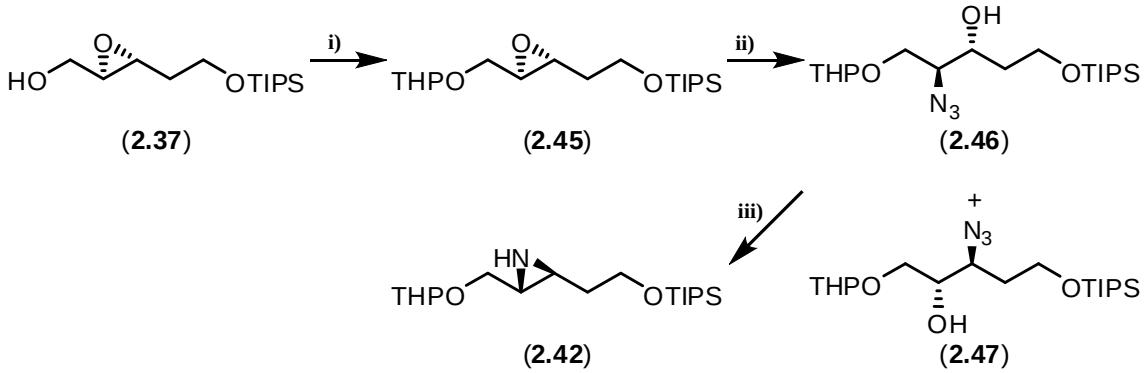
stretches. The sulphate additive was imperative to the reaction and when omitted starting materials could be recovered. The use of these labile appendages was abandoned and the tetrahydropyranyl group was chosen for the next strategy.



Reagents and Conditions: **i**. TESCl, imidazole, CH_2Cl_2, 0°C, 1 h, (97%) **ii**. CH_3OCOCl, pyridine, DMAP, CH_2Cl_2, 3 h (95%) **iii**. NaN_3, $(NH_4)_2SO_4$, MeOH/H_2O (v/v 10:3).

Scheme 2.15: Silyl and Carbonate Protections

Fortuitously the tetrahydropyranyl protection of the primary alcohol (**2.37**) proceeded smoothly in 93% yield[97]. The use of Zwanenburg and Noltes' modified Staudinger reaction on the mixture of diastereomers (**2.45**) gave both azido alcohols (**2.46**) and (**2.47**) in a combined yield of 78% (**Scheme 2.16**)[89]. Finally the mixture of organic azides was reacted with triphenylphoshine in refluxing acetonitrile which gave an almost quantitative conversion to the aziridine target molecule (**2.42**).

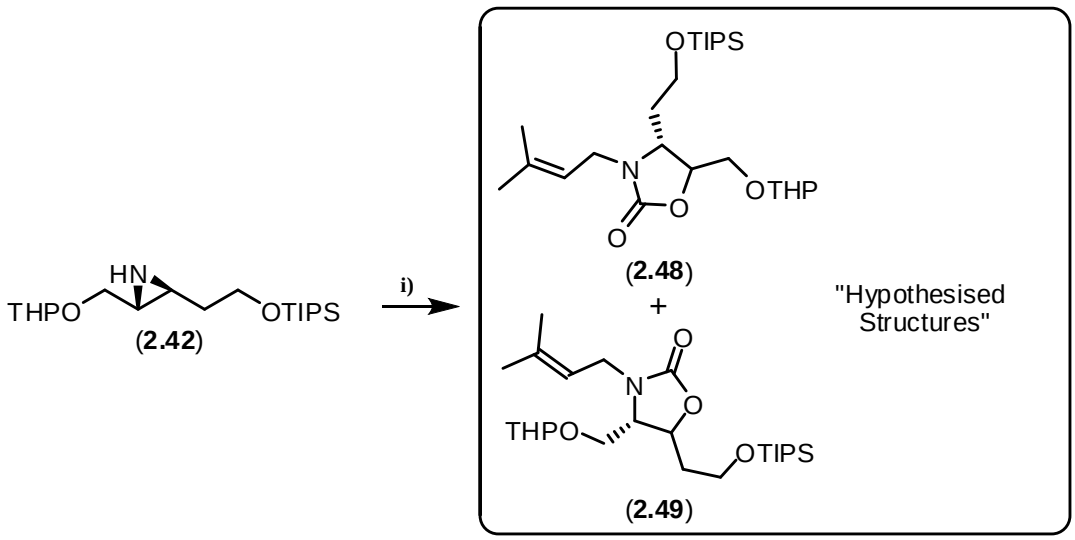


Reagents and Conditions: **i**. DHP, PPTS, CH_2Cl_2, rt, 36 h (93%), **ii**. NaN_3, $(NH_4)_2SO_4$, MeOH/H_2O (v/v 10:3) (78%), **iii**. PPh_3, MeCN, Δ, 4 h (96%).

Scheme 2.16: Formation of THP Protected Aziridine (2.42)

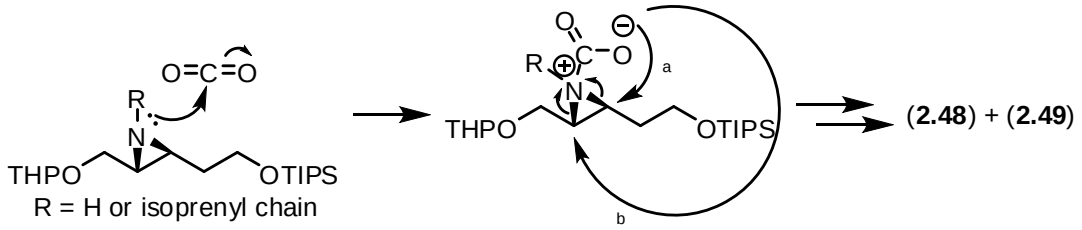
2.2.3.3 Alkylation and Deprotection Attempts on Aziridine (2.42)

Investigation into the alkylation of aziridine (**2.42**) tested the theoretical aspects behind the modified route and presented a new series of problems. Using Aggarwal's published method for alkylation of aziridines[98]; the aziridine (**2.42**) was heated with one and a half equivalents of potassium carbonate and a catalytic quantity of 18-crown-6 ether before addition of the bromide. Under these conditions two closely overlapping spots appeared by TLC. Neither of these products could be fully separated by column chromatography nonetheless, it was still possible to observe the presence of a prenyl chain. Submission of the associated masses of these compounds showed that they had additional molecular weight in the region of forty-four mass units when compared with the expected mass of the alkylated aziridine. The infrared analysis revealed the unmistakable carbonyl stretch at 1730cm^{-1} and confirmed that both *N*-alkylation and carbon dioxide insertion into the nitrogen centred 3-membered ring had occurred to form the "hypothesised" carbonylated products (**2.48**) and (**2.49**) (**Scheme 2.17**). Next, basic amberlyst® A21 ion exchange resin was used to assist in the desired alkylation step but again a similar result was recorded. Given that this sequence resulted in multi-component reaction products and the resulting structures isolated did not have the correct mass we abandoned this route and no further separations ie. by HPLC were attempted and hence these compounds have not been unequivocally assigned. A mechanism for the insertion of carbon dioxide was postulated whereby the aziridinyl nitrogen lone pair bonded to the electrophilic carbon of carbon dioxide (**Scheme 2.18**). The intermediate formed could then cyclise at either of the two major electrophilic sites (shown by arrows a and b) to form postulated products (**2.48**) and (**2.49**). The mechanism would be the same regardless of whether the alkylation step had taken place first.



Reagents and Conditions: **i**. 1-bromo-3-methyl-2-butene, 18-crown-6, K_2CO_3, MeCN, Δ, 2 h (No SM by TLC) or 1-bromo-3-methyl-2-butene, Amberlyst® A21, CH_2Cl_2, rt, 3h (No SM by TLC).

Scheme 2.17: Formation of Postulated Products (2.48 and 2.49)



Scheme 2.18: Proposed Mechanism of CO_2 Insertion

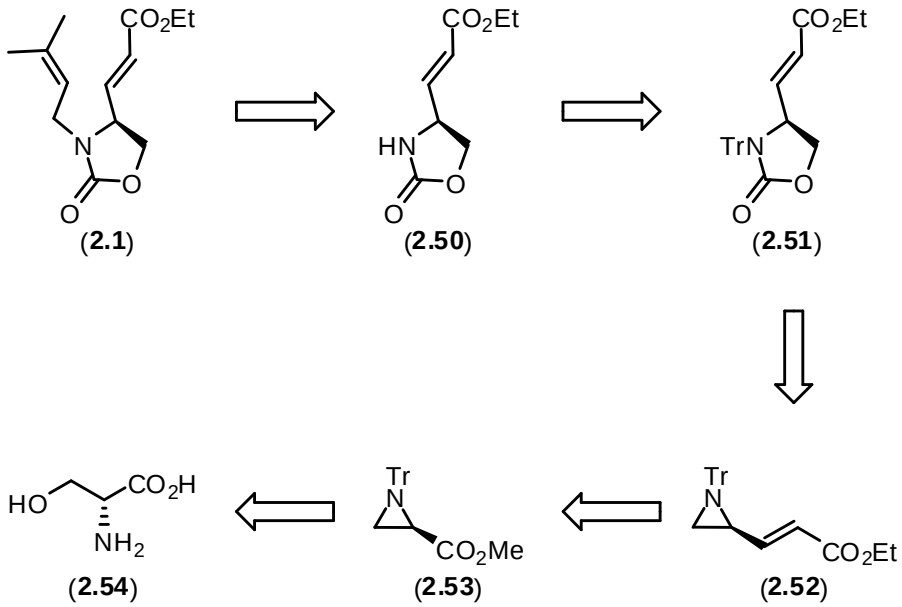
Undeterred by this complication the alkylation step was left behind with the belief that the sidechain could be coupled to our molecule after the predicted intramolecular cyclisation. Attention turned to the deprotection of the THP moiety. Acidic and reductive methods of removal were ruled out due to the sensitive groups present in the intermediate (**2.42**) so Lewis acid catalysis was the clear choice. Decaborane is known to make adducts with Lewis bases such as amino groups so this was immediately ruled out and the widely known method of magnesium bromide in diethyl ether was attempted first. Both stirring the mixture at room temperature and heating to reflux left the starting material untouched. Magnesium bromide diethyl etherate was also shown to be totally ineffective under the conditions previously described. Next it was decided to stir the aziridine with montmorrilonite K-10. This clay, named after Montmorrillon in France, is a mixture of metal silicates and has shown use in the deprotection of THP ethers when combined with some form of oxidiser[95]. However, it was proposed that it may in fact be able to remove the THP group on its own in a sufficiently mild manner to withstand sensitive substrates; but this procedure also failed. The route now proving uneconomical and inelegant and involving a variety of laborious protection and deprotection

steps was abandoned and concentration shifted toward another more successful route that had been in evaluation parallel to this direction (see ch. 2.1.5).

2.2.4 A Short Detour

2.2.4.1 Retrosynthetic Analysis 4

Intrigued by the observation of molecular carbon dioxide insertion into the aziridinyl carbon-nitrogen bonds present in intermediate molecule (**2.42**) a short exploration began to uncover whether this could serve as a simple and quick way to access the key precursor (**2.50**). From the retrosynthetic analysis (**Scheme 2.19**) it was clear that intermediate (**2.52**) could be formed by inserting a molecule of CO_2 into the aziridine ring (**2.53**) providing the correct selectivity was observed. A few simple disconnections reveals D-serine (**2.55**) which, by applying the work of Baldwin can be transformed into the enantiopure trityl protected aziridine (**2.54**) through some facile functional group manipulations and a ring closure[99].



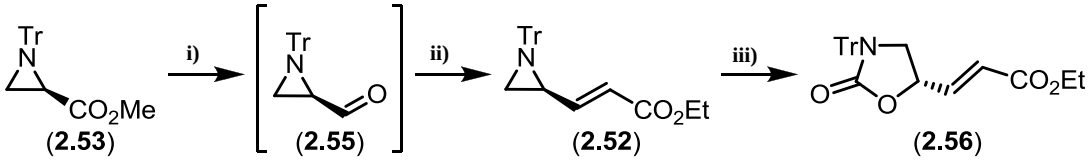
Scheme 2.19: Retrosynthetic Analysis 4

2.2.4.2 Model Study

Methyl (S)-(-)-1-tritylaziridine-2-carboxylate (**2.53**) as synthesised from D-serine (**2.54**) is commercially available and was purchased directly from Sigma-Aldrich® to test the feasibility of this route (**Scheme 2.20**). Carboxylate (**2.53**) was reduced in situ with diisobutylaluminium hydride to aldehyde (**2.55**) before undergoing a consecutive Horner-Wadsworth-Emmons olefination following the protocol highlighted by Fujii in 1995[100]. This provided us with the allylic precursor (**2.52**) in 86% yield over the 2 steps. Pinhas successfully utilised the ring

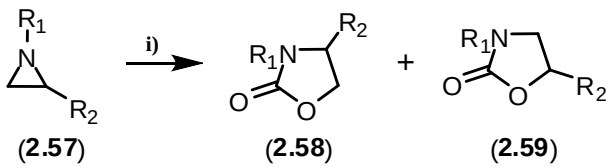
expansion of aziridines to cyclic carbamates with addition of a lithium iodide under a high pressure of gaseous CO_2[101]. He showed that a 2:1 mixture of 4-substituted 2-oxazolidinones (**2.58**) and 5-substituted 2-oxazolidinones (**2.59**) could be achieved in high yields when R_1 and R_2 are alkyl groups (**Scheme 2.21**). This is the opposite selectivity of the cyclisations between isocyanates and epoxides[75]. Pinhas also showed that if R_1 is an alkyl and R_2 is a phenyl group that exclusively the 5-substituted 2-oxazolidinone regioisomer (**2.59**) was formed. The paper concentrates on a select sample of substrates and unsure whether regioselectivity is utterly dependant on the inductive effects of substituent groups on the starting molecule, it was decided to see if this undesirable selectivity would be caused by having another electron withdrawing group at the R_2 position instead of a phenyl as with the allylic intermediate (**2.52**).

To achieve this transformation aziridine (**2.52**) was dissolved in tetrahydrofuran and one equivalent of sodium iodide was added. The entire vessel (heavy walled vial with a threaded Teflon® plug or stainless steel 'bomb') was then cooled to minus seventy-eight degrees Celsius and thirty five equivalents of powdered dry ice (carbon dioxide) were added before screwing the lid down and placing behind a blast shield to warm to room temperature. After two days the vessel was again cooled and the built up pressure carefully released before working up with 10% sodium bisulfite. On analysis the hypothesis was confirmed and solely oxazolidinone (**2.56**) was formed in 73% yield (**Scheme 2.20**). This structure can be confirmed as the chemical shift of the proton beta to the carbonyl group in compound (**2.56**) lies at 6.85 ppm. If the alternative 5-substituted structure was formed this peak would be much further upfield due to increased shielding effects of the trityl group.



Reagents and Conditions: **i**. DIBAL-H, THF, -78°C, 2 h then **ii**. Na^+ salt of $(EtO)_2P(O)CH_2CO_2Et$,THF, rt, overnight (86%), **iii**. NaI, CO_2, Sealed Vial, THF, rt, 2 days (73%).

Scheme 2.20 Formation of Oxazolidinone (2.56)



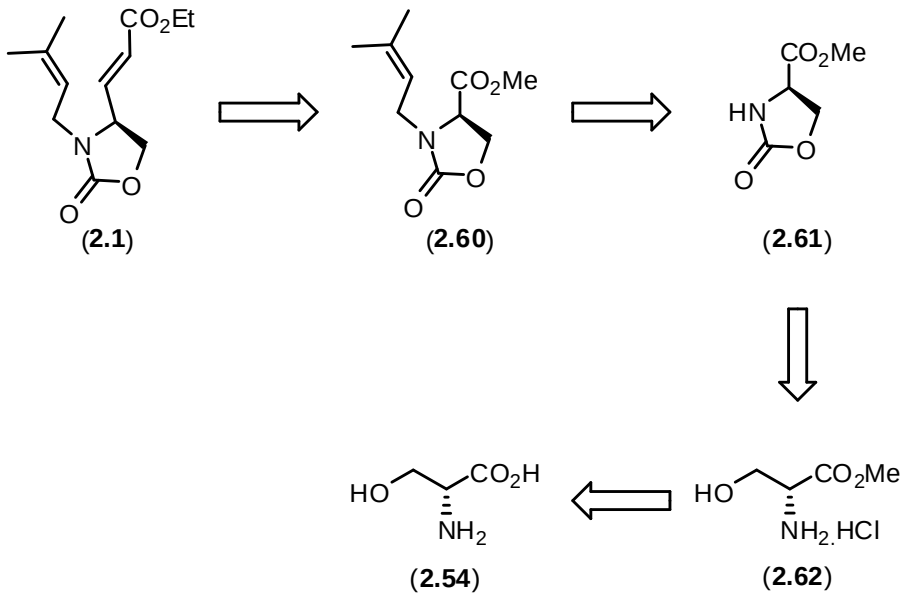
Reagents and Conditions: **i**. LiI, CO_2, sealed vial, rt, overnight.

Scheme 2.21: Pinhas' Oxazolidinone Formation[101]

2.2.5 Final Route to Ene-Precursor (2.1)

2.2.5.1 Retrosynthetic Analysis 5

The final analysis unveiled a short, concise route to precursor (**2.1**) (**Scheme 2.22**) that could provide an economically viable access to both of the kainate targets of this thesis. The allylic side chain of compound (**2.1**) could be installed following a similar reduction/alkenylation rationale used previously on aziridine (**2.53**) (see ch. 2.1.4). An alkylation brings us back to oxazolidinone (**2.61**) which can be constructed by the combination of the hydrochloride salt of D-serine methyl ester (**2.62**) and either phosgene or triphosgene. This again reveals D-serine (**2.54**) as a suitable starting material to our target molecule (**2.1**).

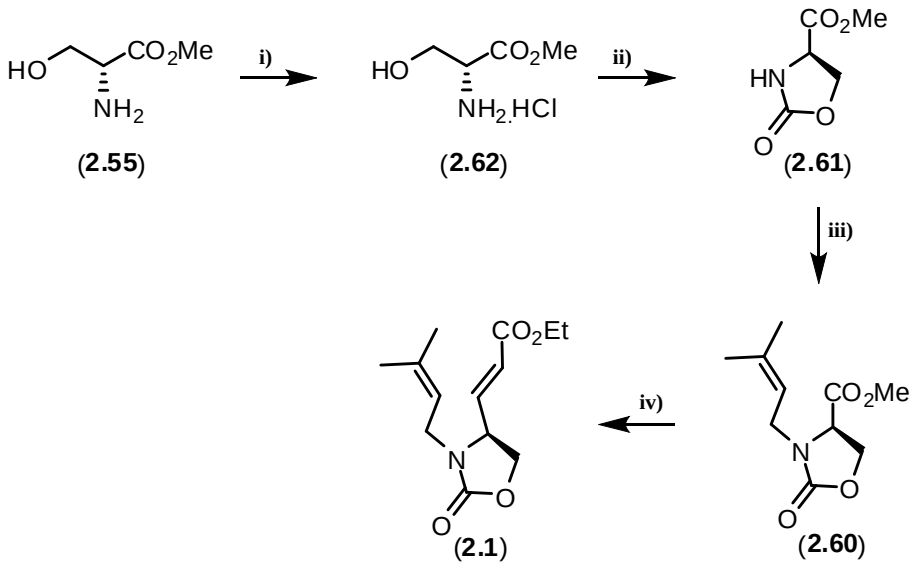


Scheme 2.22: Retrosynthetic Analysis 5

2.2.5.2 Chemistry of the Ene-Precursor (2.1)

The esterification of D-serine with acidified methanol proceeded smoothly to furnish ester (**2.62**) in an 89% yield (**Scheme 2.23**)[102]. With the hydrochloride salt (**2.62**) in hand a minor adjustment of Nudelman's protocol[103] was used to react with triphosgene and quantitatively convert (**2.62**) to the core oxazolidinone (**2.61**). The next step was to investigate the *N*-allylation of compound (**2.61**). Another paper published by Nudelman et al. in 1994[104] showed that the alkylation should proceed easily with sodium hydride in dimethylformamide. Unfortunately the yields recorded with 3,3-dimethylallyl bromide were initially vastly lower than hoped for at around 44%. Following an exploration into a few alternative solvents such as tetrahydrofuran[105] (11-49% yield depending on the batch of sodium hydride used) and diethyl ether (21% yield), an optimal 4:1 mixture of THF and DMF was reached as a reaction solvent.

The low yields and inconsistency of this step can be attributed to the low solubility of the sodium salt of intermediate (**2.61**) in THF and diethyl ether. Addition of DMF as a co-solvent aided solvation and allowed for complete deprotonation before the addition of prenyl bromide. With these vital adjustments, the yield associated with this previously uneconomical step increased to a more manageable 78%. Fujii's DIBAL-H reduction[100] and a synchronal Wittig olefination complete the synthesis of the previously unknown key intermediate (**2.1**). The ^{1}H-NMR of the Ene-precursor molecule is shown below (**Figure 2.8**).



Reagents and Conditions: **i**. CH_3COCl, MeOH, Δ, 3 h (89%), **ii**. Et_3N, triphosgene, CH_2Cl_2, 0°C-rt, 24 h (quantitative), **iii**. NaH THF:DMF (4:1 v/v), 1-bromo-3-methyl-2-butene, 0°C-rt, 16 h (78%), **iv**. a) DIBAL-H, CH_2Cl_2, -78°C b) NH_4Cl, $(C_6H_5)_3P{=}CHCO_2CH_3$, -78°C-rt, 18 h (83%).

Scheme 2.23: Formation of Ene-Precursor (2.1)

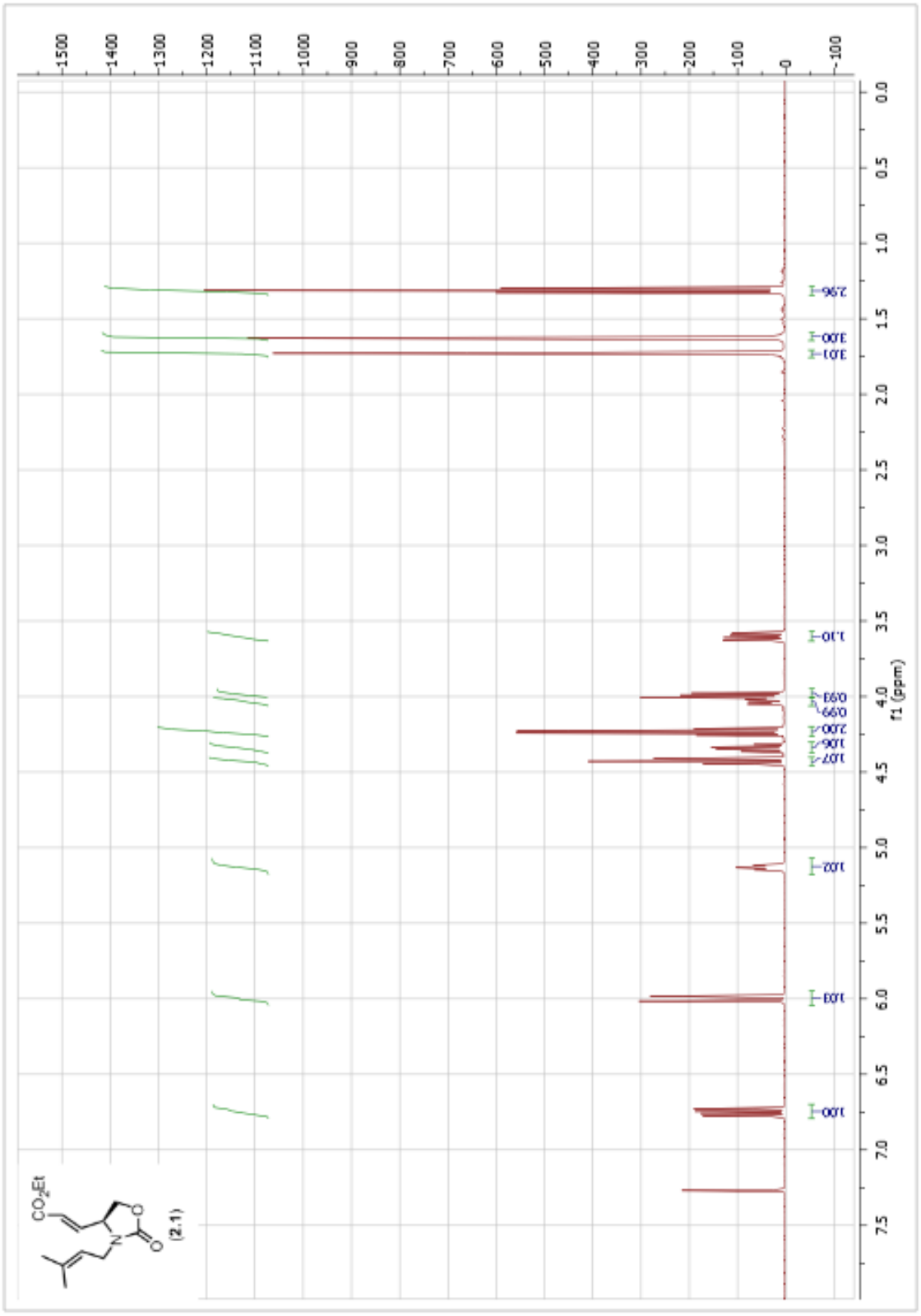
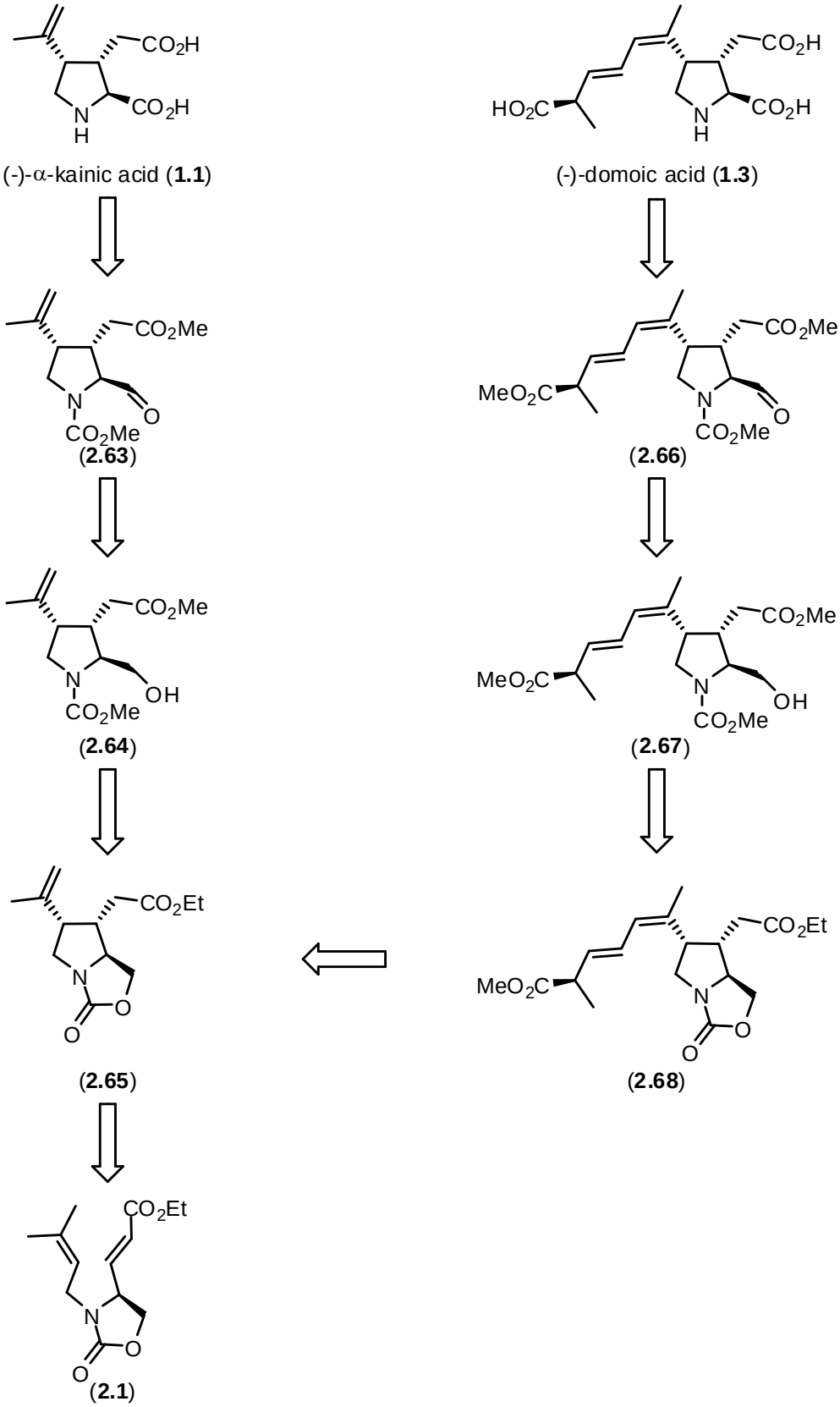


Figure 2.8: ^{1}H-NMR of Ene-Precursor Compound (2.1)

2.32 Investigating the Synthesis of Kainic Acid (1.1) and Domoic Acid (1.3)

2.3.1 Retrosynthesis

It was envisaged that rapid progress towards kainic acid (**1.1**) and domoic acid (**1.3**) could be made utilising an intramolecular ene-reaction on the key precursor (**2.1**) (**Scheme 2.24**). The synthesis now splits into two lateral routes. Ene-product (**2.65**) could undergo a cross metathesis of the isoprenyl double bond to install an octadienic sidechain allowing access to domoic acid precursor (**2.68**). To reach the final targets would then require parallel base mediated carbamate ring opening, re-esterification and *N*-protection of products (**2.65**) and (**2.68**) to furnish alcohols (**2.64**) and (**2.67**). Careful oxidation of the primary alcohol functionality on both molecules (**2.64**) and (**2.67**) to aldehyde products (**2.63**) and (**2.66**), followed by an end game oxidation and global deprotection would yield target molecules (-)-(α)-kainic acid (**1.1**) and (-)-domoic acid (**1.3**).



Scheme 2.24: Retrosynthetic Analysis 5

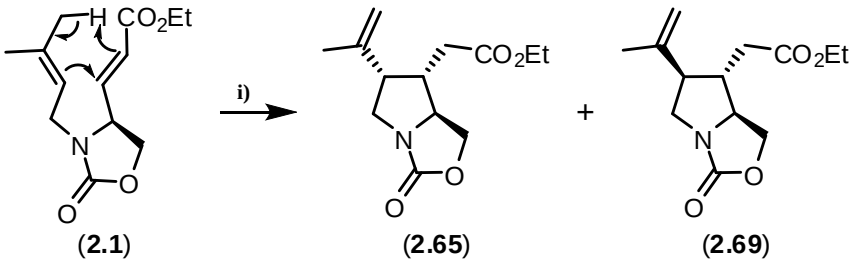
2.3.2 The Ene-Reaction and Microwave Chemistry

2.3.2.1 History of the Ene-Reaction

The ene-reaction was first identified by Alder in 1943[106]. Since then it has received a great deal of interest with respect to a large variety of substrates[107-109] and moreover in the synthesis of a number of natural products including kainic acid (**1.1**)[17,34,35,37,40]. The intramolecular version of this concerted 6-electron pericyclic reaction occurs between an allylic hydrogen (ene) and electron deficient π-bond (enophile). Ene-reactions are renowned for having higher activation energies than the related Diels-Alder cyclisation and thus higher reaction temperatures are generally required. These harsh conditions and long reaction times saw some major pitfalls in the past such as unwanted by-products and the use of high boiling solvents or high pressures. These factors thus hindered the widespread use of the ene-reaction in organic synthesis[109]. Conveniently microwave irradiation has grown in popularity in recent years as a far more efficient way of heating[110-112]; this has reduced the need for such elevated reaction temperatures and in some cases completely removed the need for solvent.

2.3.2.2 The Ene-Reaction of Oxazolidinone (2.1)

An extensive investigation was undertaken with respect to the diastereoselective cyclisation of ene-precursor (**2.1**) (**Tables 2.4-2.6**). With the oxazolidinone ring installed, precursor (**2.1**) could be converted into a mixture of both the desired *cis*-product (**2.65**) and unwanted *trans*-product (**2.69**) in good yields and reasonable selectivity (**Scheme 2.25**). It was hoped at this stage that the undesired *trans*-product could be removed in the crystallisation process of both target molecules (**1.1**) and (**1.3**) at the end of the synthesis so, from here on the compounds have been treated as if they were purely of *cis*-stereochemistry.



Reagents and Conditions: **i**. See **Tables (2.4-2.6).**

Scheme 2.25: Ene-Reaction Major Products

Oppolzer and Thirring's reaction conditions were chosen as a starting point[17] (**Table 2.4**). Unfortunately after 24 hours at 130°C in toluene, no reaction had occurred (entry 1) so the

temperature was increased to 180°C in toluene but after 48 hours only 25% of the starting material had been converted and a product distribution of only 3:1 in favour of diastereoisomer (**2.65**) was seen by ^{1}H-NMR analysis (entry 2). The ene-reaction proceeded in *p*-xylene with a comparatively good ratio of *cis* to *trans*-products; however the reaction times were not suitable (entry 3). After attempting the cyclisation in DMF and receiving disappointing results (entry 4), solvent free options were explored. On a small scale (<101mg) the reaction progressed at various temperatures however the yields and selectivity were both unsatisfactory (entries 5-9). It was also found that this protocol was not scaleable and simply led to molecular decomposition in the microwave's heating time (entry 10).

Entry	Solvent	Temp (°C)	Scale/Conc.	Time	Combined yield	Ratio (2.65:2.69)
1	Toluene	130	5%	24 h	No Reaction	N/A
2	Toluene	180	5%	48 h	Trace	3:1
3	^{p}Xylene	170	1 g in 20 mL	65 h	62	5:1
4	DMF	180	100 mg in 2 mL	1.5 h	50	3:1
5	Neat	120	302 mg	1 h	No Reaction	N/A
6	Neat	150	302 mg	20 h	30	3:2
7	Neat	200	100 mg	56 m	55	4:1
8	Neat	250	100 mg	2 m	48	3:1
9	Neat	300	100 mg	1 m	30	4:1
10	Neat	300	>600 mg	30 s	Decomp.	N/A

Table 2.4: Investigation of Microwave-Induced Ene-Reaction Entries 1-10

In the laboratory *N*,*N*-diethylaniline had been found to be a reliable high boiling solvent for another series of microwave reactions and that removal was easily performed through column chromatography on silica following the reaction. This choice of solvent was discovered to be exceptional as long as the substrate was not too concentrated (**Table 2.5**). Higher concentrations and longer reaction times seemed to cause the *cis*-product to decompose at a greater rate from that of the *trans*-product and so yield and the diastereomeric ratio decreased if time and temperature were not controlled. It was found that by increasing the reaction temperature to around 200°C in DEA and increasing the reaction time to around 4 hours gave an optimal return and highest selectivity towards the desired target (**2.65**) (entry 12). It must be noted that used caps on the microwave vessel were not suitable for high temperature reactions. This observation is possibly due to not forming a tight seal and therefore not being able to hold the pressure as efficiently as new seals. When use of old seals cannot be avoided reaction times must be increased appropriately. It was pleasing to find that even at a reduced temperature and

longer reaction time in the microwave, selectivity decreased only marginally but in fact produced a better yield of products (**2.65** and **2.69**) (entry 13). The highest temperature of reaction in DEA shown (entry 11) was only attainable when using the smaller 15 mL microwave vials. This elevated temperature could not be reached when using the larger volume 35 mL vials. This reaction was thereafter performed in 1 gram batches in 20 mL of DEA heated to 200 degrees Celsius for four hours. The crude reaction mixtures were combined and collectively columned.

Entry	Solvent	Temp (°C)	Scale/Conc.	Time	Combined yield	Ratio (2.65:2.69)
11	DEA	242	500 mg in 10mL	2 h	78	5:1
12	**DEA**	**200**	**1 g in 20 mL**	**4 h**	**80**	**7:1**
13	DEA	190	1 g in 20 mL	4.5 h	86	6:1
14	DEA/MeCN	259	500 mg in 2.5 mL	2 h	49	3:1

Table 2.5: Investigation of Microwave–Induced Ene-Reaction Entries 11-14

A selection of Lewis acid catalysts including tin, gold and diethylaluminium chlorides were also examined however the addition of these compounds did not assist in decreasing the activation barrier to this reaction and no products were found (entries 15-17).

Entry	Solvent	Temp (°C)	Scale/Conc.	Catalyst	Time	Combined yield	Ratio (2.65:2.69)
15	CH_2Cl_2	-78-rt	100 mg in 10mL	$SnCl_4$	16 h	No Reaction	N/A
16	CH_2Cl_2	Rt	100 mg in 10 mL	$AuCl_3$	48 h	No Reaction	N/A
17	CH_2Cl_2	0-rt	100 mg in 10 mL	Et_2AlCl	24 h	No Reaction	N/A

Table 2.6: Investigation of Ene-Reaction Entries 15-17

2.3.3 The Cross Metathesis Reaction

2.3.3.1 History and Literature Precedents for Cross Couplings

Olefin metathesis is one of the most important carbon-carbon bond forming tools used in organic synthesis. In 2005 the Nobel Prize[113] was given for the pioneering work of Chauvin, Grubbs and Schrock who provided both the mechanism[114] and a variety of ruthenium[115-118] and molybdenum[119,120] based catalysts suited for the methathesis of a wide range of substituted olefins. Intense research in this area has provided a general model for predicting the selectivity and stereoselectivity of product formation in olefin cross metathesis (CM) based on the olefins

reactivity. These reactivities are dependant on the molecules propensity to homodimerise and are classed as shown (**Figure 2.9**)[121].

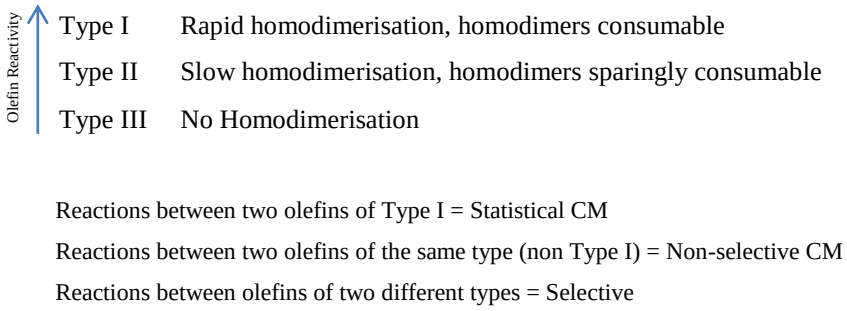


Figure 2.9: Olefin Classes and Selectivity Rules[121]

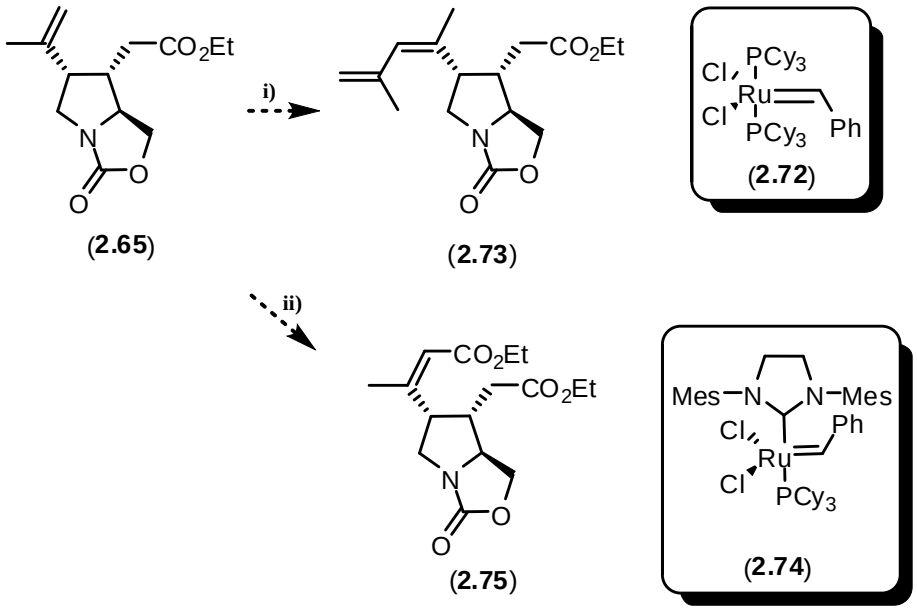
Based on these precedents two readily available Type I alkenes; isoprene (**2.70**) and ethyl acrylate (**2.71**) (**Figure 2.10**) were chosen as partners to be reacted with the Type III metathesis precursor (**2.65**).

(**2.70**) (**2.71**)

Figure 2.10: Type I Olefins

2.3.3.2 Investigation into Metathesis of Isoprenyl group

A brief model study utilising the selection of readily available unsaturated molecules was conducted to examine the general feasibility of this approach (**Scheme 2.26**). The metathesis precursor (**2.65**) was first subjected to 10 mol % of Grubbs' 1st generation catalyst (**2.72**)[115,118] in an excess of isoprene (**2.70**) at room temperature. These were found to be inadequate conditions for the formation of cross-metathesis product (**2.73**), so the more robust Grubbs' 2nd generation catalyst (**2.74**)[116,117] was tested and this produced a similar result. Despite increased catalyst loading and heating to reflux in dichloromethane, only starting material (**2.65**) was recovered. Isoprene was substituted for ethyl acrylate (**2.71**) and on treatment with Grubbs II under reflux conditions in dichloromethane was found also to be ineffective at allowing conversion to the predicted product (**2.73**). Due to limited time a thorough investigation into the metathesis of the isoprenyl group has yet to be completed.

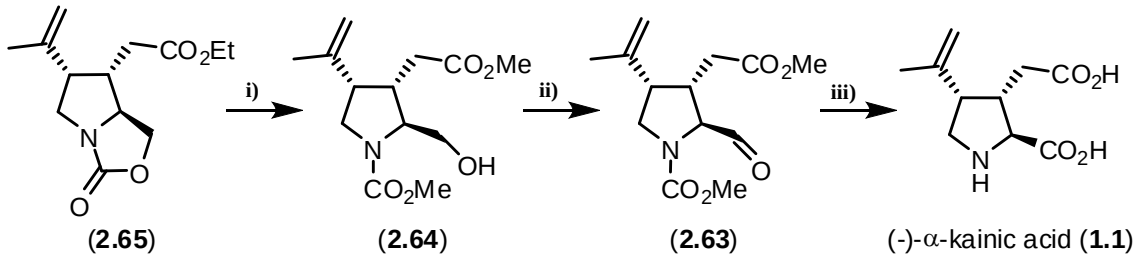


Reagents and Conditions: **i**. Grubbs I (**2.57**) or Grubbs II (**2.59**), isoprene (**2.70**) CH_2Cl_2, Δ, 6 h (no reaction), **ii**. Grubbs II (**2.59**), ethyl acrylate (**2.71**), CH_2Cl_2, Δ, 16 h (no reaction).

Scheme 2.26: Investigation of Cross-Metathesis

2.3.4 Final Manipulations to (-)-(α)-Kainic Acid (1.1)

A concurrent *trans*-esterification, ring-opening and *N*-carbamate protection was achieved in one-pot with a catalytic amount of caesium carbonate in methanol[122] to furnish alcohol (**2.64**) in 80% yield (**Scheme 2.27**). Alcohol (**2.64**) was then converted into aldehyde (**2.63**) in good yield (82%) through the use of a Parikh-Doering oxidation[123]. A similar partial oxidation was attempted with Fetizon's reagent (silver carbonate on Celite®) but no reaction occurred[124]. The synthesis was completed using a second oxidation with sodium chlorite to introduce the C-2 carboxyl group[125], a subsequent deprotection of the crude acid with sodium hydroxide and final purification using ion-exchange chromatography[17] constructed the final target molecule (-)-(α)-kainic acid (**1.1**) in 60 % yield from the aldehyde (**2.63**). All of the data collected for this molecule matches that previously published[63]. The crystal structure as determined by x-ray crystallography is included as proof (**Figure 2.11**).



Reagents and Conditions: **i**. Cs_2CO_3, MeOH, rt, 5 d (80%), **ii**. py.SO_3, Et_3N, DMSO, CH_2Cl_2, 0°C-rt, 16 h (89%), **iii**. 1) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH, H_2O, rt, 16 h, 2) $NaOH_{(aq)}$, MeOH, Δ, 18 h, 3) Ion-exchange chromatography (60% from aldehyde).

Scheme 2.27: Final Manipulations to (-)-(α)-Kainic Acid (1.1)

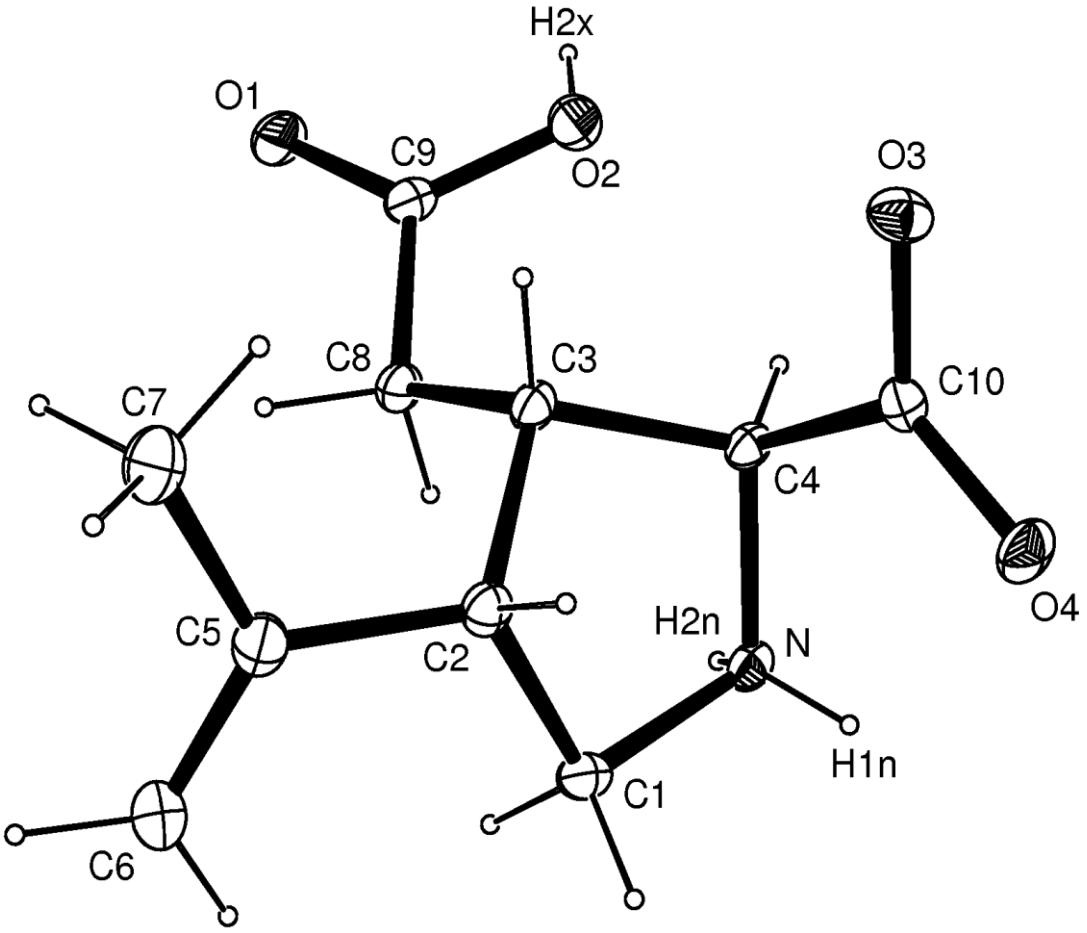
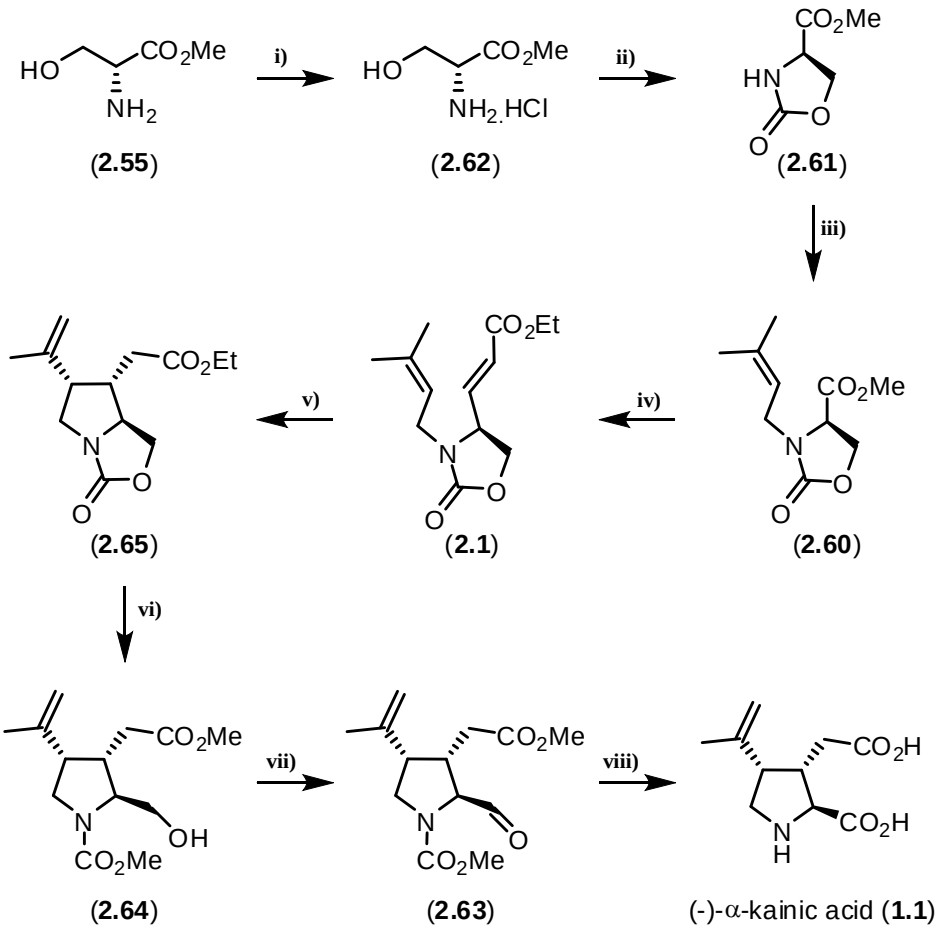


Figure 2.11: X-ray Structure of (-)-(α)-Kainic Acid (1.1)

2.4 Conclusion

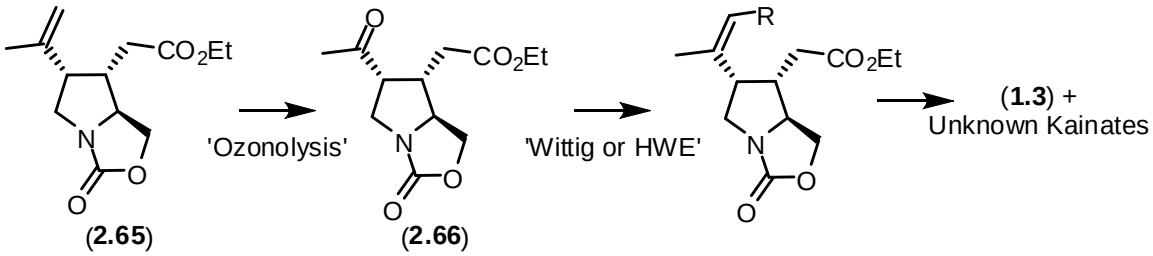
The usefulness of oxazolidinone (**2.1**) as a key precursor for the synthesis of biologically important molecules has been demonstrated in a new highly stereoselective total synthesis of (-)-α-kainic acid (**1.1**). Two new stereocentres have been created with complete control in an eight step synthesis from D-serine (**2.55**) (**Scheme 2.28**). A total of three dead-ends and one detour were explored before a viable and economical access to the valuable target molecule (**1.1**) was found. The final route gave kainic acid (**1.1**) in an overall yield of 20%; some of the intermediates yields could still be improved. Huang *et al*. has reported a quantitative conversion of D-serine (**2.55**) to the methyl ester (**2.62**)[126] and the addition of heat to the ring opening of ene-product (**2.65**) may allow for a faster reaction times and an improvement in yield. Finally a number of different oxidations for the conversion of alcohol (**2.64**) to aldehyde (**2.63**) should also be trialed.



Reagents and Conditions: **i**. CH_3COCl, MeOH, Δ, 3 h (89%), **ii**. Et_3N, triphosgene, CH_2Cl_2, 0°C-rt, 24 h (quantitative), **iii**. NaH THF:DMF (4:1 v/v), 1-bromo-3-methyl-2-butene, 0°C-rt, 16 h (78%), **iv**. a) DIBAL-H, CH_2Cl_2, -78°C b) NH_4Cl, $(C_6H_5)_3P{=}CHCO_2CH_3$, -78°C-rt, 18 h (83%). **v**. DEA, 200°C, 4 h (80%) **vi**. Cs_2CO_3, MeOH, rt, 5 d (80%), **vii**. py.SO_3, Et_3N, DMSO, CH_2Cl_2, 0°C-rt, 16 h (89%), **viii**. 1) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH, H_2O, rt, 16 h, 2) $NaOH_{(aq)}$, MeOH, Δ, 18 h, 3) Ion-exchange chromatography (60% from aldehyde).

Scheme 2.28: Final Route to Kainic Acid (1.1)

Neither introduction of the octadiene sidechain found in (-)-domoic acid (**1.3**) or novel sidechains have been realised as attempts to cross metathesise the isoprenyl unit failed to give any new products. It is hoped that a solution to this problem can be found by undertaking a more extensive investigation into the chemistry of the terminal alkene. An ozonolysis and sequential Wittig or Horner-Wadsworth-Emmons olefination on the resultant aldehyde (**2.66**) provides an alternative means of access to this potent alkaloid and many unknown kainates (**Scheme 2.29**).



Scheme 2.29: Proposed Future Route to Domoic Acid (1.3) and Novel Kainates

CHAPTER 3: Experimental

3.1 General Experimental Procedures

All reactions were conducted under a nitrogen atmosphere unless otherwise stated, using oven dried glassware. Reactions requiring anhydrous conditions were carried out using flame-dried glassware under nitrogen.

Analysis by thin layer chromatography was carried out using Machery Nagel glass backed plates pre-coated with a 0.25 mm layer of UV254 silica gel. Visualization was possible by ultraviolet radiation (254 nm), potassium permanganate or vanillin dips. Purification by flash column chromatography was carried out using Fisher Davisil® 60Å silica gel (particle size 35-70 micron) or Sigma-Aldrich® 60Å technical grade silica gel (particle size 200-425 mesh pH 6.5-7.5) eluting with solvents commercially available from Fisher scientific.

Melting points were recorded using a Gallenkamp melting point apparatus and are uncorrected.

^{1}H-NMR spectra were recorded using a Varian 500 instrument at 500 MHz. Samples were run in deuterochloroform, deutero DMSO or deuterium oxide at 30 °C and are referenced to a deuterochloroform, deutero DMSO or deuterium oxide internal references respectively. Chemical shifts are measured in ppm on the δ scale and coupling constants (*J*) are measured in Hertz. The following abbreviations were used to represent multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet, doublet, doublets; dt, doublet of triplets; td, triplet of doublets; br, broad; app, apparent.

^{13}C-NMR spectra were recorded using a Varian 500 instrument at 126 MHz. Samples were run in deuterochloroform, deutero DMSO or deuterium oxide, at 30 °C and are referenced to a deuterochloroform, deutero DMSO or deuterium oxide internal references respectively. Chemical shifts are measured in ppm on the δ scale. DEPT, COSY, ROESY, HSQC and HMBC experiments were run in conjunction with the ^{13}C NMR to aid assignment.

Low and high resolution mass spectra were recorded on a Fisons Instrument VG Autospec mass spectrometer. The following abbreviations were used to describe the experiment: EI^{+}, electron impact; ESI^{+}, electron spray ionisation; LRMS low resolution mass spectrometry; HRMS, high resolution mass spectrometry.

Infrared spectra were recorded on a Perkin-Elmer 1710 Fourier transform spectrometer with a diamond attenuated total reflectance attachment.

Microwave enhanced reactions were conducted using thick-walled glass tubes in a CEM Corporation® Discovery NP-1009 300W microwave system.

Chemical reagents were commercially available and used without any further purification unless otherwise stated.

All organic solvents were freshly distilled under a nitrogen atmosphere unless otherwise stated from an appropriate drying agent as described below:

Solvent	Drying Reagent
Acetonitrile, dichloromethane, benzene, ethyl acetate, *N*,*N*-dimethylformamide[a]	Calcium hydride
Tetrahydrofuran, diethyl ether	Sodium (in the presence of benzophenone)
Ethanol, methanol	Magnesium turnings[b]

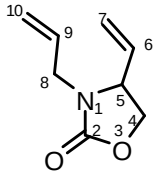
[a] Under reduced pressure.

[b] Magnesium turnings were first activated by heating with a crystal of iodine under a nitrogen atmosphere.

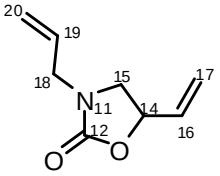
All compounds mentioned in the following experimental were specifically numbered to aid in the identification of protons and carbons in the relevant spectra. They do not necessarily correspond with that of the I.U.P.A.C. guidelines.

3.2 Compound Data

Preparation of 3-allyl-4-vinyl-1,3-oxazolidin-2-one (2.11) and 3-allyl-5-vinyl-1,3-oxazolidin-2-one (2.12)



(**2.11**)



(**2.12**)

These known compounds were synthesised as a mixture using a modification of the procedure according to Herweh *et al.*[75].

To a stirring solution of LiCl (100 mg, 2.3 mmol) in DMF (20 mL) was added 3,4-epoxy-1-butene (**2.10**) (900 mg, 12.8 mmol) in 1 portion, at rt. The resulting solution was heated to reflux and allyl isocyanate (**2.9**) (1.06 mL, 12 mmol) was added dropwise. The resulting solution held at reflux for 6 h, after this time water (40 mL) was added and the organic components extracted using diethyl ether (3 x 20 mL). The solution was then dried, ($MgSO_4$) concentrated under reduced pressure and purified via flash chromatography eluting with hexanes/diethyl ether (1:1) to afford an inseparable mixture of the title compounds (**2.11**) and (**2.12**) in a (1:2.5 ratio) respectively (1.1 g, 60 %) as a yellow liquid.

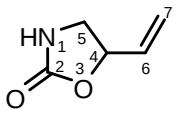
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89-5.79 (m, 2.5H, H19), 5.75 – 5.67 (m, 3.5H, H7/H17), 5.66 – 5.58 (m, 1H, H6), 5.41 – 5.07 (m, 14H, H7/H9/H10/H16/H17/H20), 4.91 – 4.82 (m, 2.5H, H14), 4.37 (dd, *J* = 8.5, 8.5 Hz, 1H, H4), 4.19 (dt, *J* = 8.5, 8.5 Hz, 1H, H5), 4.07 – 4.00 (m, 1H, H8), 3.95 – 3.86 (m, 1H, H4), 3.86 – 3.72 (m, 5H, H18), 3.64 – 3.57 (m, 2.5H, H14), 3.46 (app. dt, *J* = 15.5, 7.5 Hz, 1H, H8), 3.18 (dd, *J* = 8.5, 8.5 Hz, 2.5H, H14).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7(C12), 157.5 (C2), 134.5 (C19), 134.5 (C6), 131.9 (C17), 131.7 (C9), 121.2 (C7), 121.2 (C16), 118.6 (C20), 118.5 (C10), 73.7 (C14), 67.1 (4), 58.5 (C5), 49.5 (C15), 46.8 (C18), 44.4 (C18).

ν_{max} (FTIR)cm^{-1}: 2983 (C-H), 1741 (C=O), 1711 (C=C), 1415, 1248 (C-N).

HRMS (ESI^+): calcd for $C_8H_{11}O_2NNa$, *m/z* = 176.0682, found 176.0686.

Preparation of 4-vinyl-1,3-oxazolidin-2-one (2.14)



(**2.14**)

This known compound was synthesised using a modification of the procedure according to Herweh *et al.*[75].

To a stirring solution of 3,4-epoxy-1-butene (**2.10**) (522 mg, 7.5 mmol) in CH_2Cl_2 (20 mL) at rt was added dropwise chlorosulfonyl isocyanate (**2.13**) (1 g, 7.1 mmol). The resulting solution was left to stir for 6 h. After this time saturated $KI_{(aq)}$ solution (15 mL) was added and the organic components separated and washed with a saturated solution of saturated $NH_4Cl_{(aq)}$ (20 mL) then water (20 mL). The solution was then dried, ($MgSO_4$) concentrated under reduced pressure and purified via flash chromatography eluting with hexanes/diethyl ether (1:4) to afford the title compound (**2.14**) (411 mg, 51 %) as a brown liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (app. ddd, *J* = 17.2, 10.4, 6.9 Hz, 1H, H6), 5.49 (d, *J* = 17.1 Hz, 1H, $H7_{cis}$), 5.42 (d, *J* = 10.4 Hz, 1H, $H7_{trans}$), 5.11 (app. q, *J* = 7.5 Hz, 1H, H4), 4.58 (app. t, *J* = 8.3 Hz, 1H, H5), 4.14 (dd, *J* = 7.5, 16.0 Hz, 1H, H5).

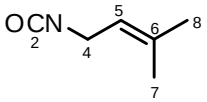
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7 (C2), 132.2 (C6), 121.1 (C7), 77.3 (C4), 69.1 (C5).

ν_{max} (FTIR)cm^{-1}: 3576 (N-H), 2991 (C-H), 2922 (C-H), 1781(C=O), 1160 (C-O), 1052 (C-N).

LRMS (EI$^+$): *m/z* = **114 (34%)** (Deuterated Form), 97 (18%), 69 (20%), 55 (24%), 54 (100%).

R_f = 0.21 (1:1 diethyl ether : hexanes).

Preparation of 1-isocyanato-3-methyl-2-butene (2.4)



(**2.4**)

This known compound was synthesised using a modification of the procedure according to Chrisophersen *et al.*[72].

To a stirring suspension of silver cyanate (10 g, 67 mmol) in diethyl ether (35 mL) at rt in a darkened flask was added dropwise 1-bromo-3-methyl-2-butene (**2.8**) (10 g, 67 mmol). The

resulting solution was left stirring 2 h. After this time the solution was filtered through Celite® (500 fine) concentrated under reduced pressure and distilled (118 °C @ 20 mbar) to afford the title compound (**2.4**) (3.83 g, 51 %) as a colourless liquid.

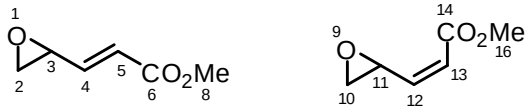
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.31 (t, *J* = 7.0 Hz, 1H, H5), 3.82 (d, *J* = 7.0 Hz, 2H, H4), 1.75 (s, 3H, H7), 1.68 (s, 3H, H8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 136.9 (C2), 120.1 (C5), 40.5 (C4), 30.5 (C6), 25.4 (C7), 17.7 (C8).

ν_{max} (FTIR)cm^{-1}: 2976 (C-H), 2254 (N=C=O).

LRMS (EI^{+}): *m/z* = **111 (35%)**, 97 (53%), 95 (43%), 85 (44%), 84 (38%), 83 (55%), 81 (55%), 71 (55%), 69 (100%), 57 (78%), 55 (60%).

Preparation of methyl (2*Z*)-3-oxiran-2-ylacrylate and methyl (2*E*)-3-oxiran-2-ylacrylate (2.16)



(**2.16**)

These known compounds were synthesised as a mixture using a modification of the procedure according to Font *et al.*[71].

To a stirring solution of $H_2O_{2(aq)}$ (35 wt.%) (16.5 g, 170 mmol) in water (60 mL) adjusted to pH 8.0 by addition of a few drops 1M $NaOH_{(aq)}$ at rt was added dropwise acrolein (**2.7**) (10.1 g, 170 mmol) whilst keeping temperature between 25-35 ºC and maintaining a pH of 8.0-8.5 through slow addition of 1M $NaOH_{(aq)}$. After 1 h at rt, (pH 8.0-8.5) the crude mixture was added dropwise to a stirring suspension of (triphenylphosphoranylidene) acetate (50 g, 145 mmol) in MeOH (215 mL) at 0 ºC. Continuous addition of 1M $NaOH_{(aq)}$ to dropping funnel maintained pH of crude epoxidation mixture. Reaction was warmed to rt and left stirring overnight. After this time MeOH was removed under reduced pressure and aqueous solution was extracted with diethyl ether (3 x 50 mL). Following repeated crystallisation and filtration of organics until no more triphenylphosphine oxide precipitated the residue was distilled (58 °C @ 0.5 mbar) to afford the title compounds (**2.16**) (10.6 g, 46 %) as a colourless liquid in a 1:2 ratio of *cis*:*trans* stereoisomers.

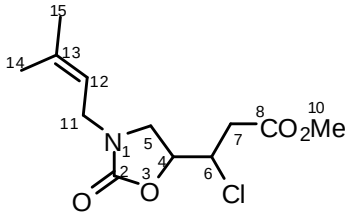
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (dd, *J* = 15.7, 7.3 Hz, 0.5H, H12), 6.19 (d, *J* = 15.7 Hz, 0.5H, H13), 6.02 (dd, *J* = 11.6, 0.6 Hz, 1H, H4), 5.75 (dd, *J* = 11.6, 8.4 Hz, 1H, H5), 4.60 – 4.52 (m, 1H, H3), 3.77 (s, 3H, H8), 3.76 (s, 1.5H, H16), 3.49 – 3.43 (m, 0.5H, H11), 3.11 (dd, *J* = 5.3, 4.5 Hz, 1H, H2), 3.06 (dd, *J* = 5.5, 4.2 Hz, 0.5H, H10), 2.72 (dd, *J* = 5.5, 2.3 Hz, 0.5H, H10), 2.70 (dd, *J* = 5.5, 2.6 Hz, 1H, H2).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.2 (C6), 165.9 (C14), 146.9 (C5), 145.0 (C13), 123.8 (C12), 123.7 (C4), 51.7 (C16), 51.5 (C8), 50.2 (C11), 49.2 (C3), 48.1 (C2), 48.0 (C10).

v_{max} (FTIR)cm^{-1}: 2997 (C-H), 2955 (C-H), 1717 (C=O), 1647 (C=C), 1440 (C-H), 1200 (C-0), 1180 (C-O_{ester}).

HRMS: calcd for $C_6H_8O_3Na$, *m/z* = 151.0351, found 151.0365.

Preparation of methyl 3-chloro-3-[3-(3-methylbut-2-en-1-yl)-2-oxo-1,3-oxazolidin-5-yl] propanoate (2.18)



(**2.18**)

This unknown compound was synthesised using a modification of the procedure according to Herweh *et al.*[75].

To a stirring solution of epoxide (**2.16**) (551 mg, 4.3 mmol) in DMF (10 mL) was added $CaCl_2$ (150 mg, 1.4 mmol) in 1 portion, at rt. The resulting solution was placed in a silicon oil bath at 160 ºC and once all solid had dissolved 3,3-dimethylallyl isocyanate (**2.4**) was added dropwise. The resulting solution was held at reflux for 6 h, after this time the reaction was cooled and water (50 mL) was added. The organic components were extracted using diethyl ether (3 x 30 mL) washed with saturated $NaCl_{(aq)}$ (1 x 25 mL) then dried, ($MgSO_4$) concentrated under reduced pressure and purified via flash chromatography eluting with hexanes/diethyl ether (1:1) to afford the title compound (**2.18**) as single diasteromer (based on ^{1}H-NMR data) (45 mg, 4 %) as a brown liquid.

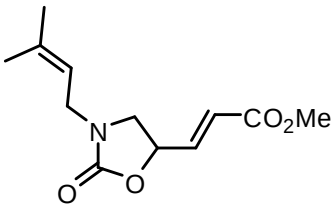
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (t, *J* = 7.1 Hz, 1H, H12), 4.5 (app. q, *J* = 4.0 Hz, 1H, H4), 4.06 (dd, *J* = 6.2, 15.5 Hz, 1H, H11), 3.96 (dt, *J* = 8.95, 3.9 Hz, 1H, H6), 3.75 (d, *J* = 4.1 Hz, 2H, H5), 3.71 (s, 3H, H10), 3.67 (dd, *J* = 15.5, 7.7 Hz, 1H, H11), 2.78 (dd, *J* = 3.7, 16.4 Hz, 1H, H7), 2.56 (dd, *J* = 9.1, 16.4 Hz, 1H, H7), 1.74 (s, 3H, H14), 1.70 (s, 3H, H15).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3 (C8), 156.3 (C2), 137.9 (C13), 117.7 (C12), 76.9 (C4), 54.2 (C6), 52.0 (C10), 45.4 (C5), 40.1 (C11) 37.0 (C7), 25.6 (C14), 17.9 (C15).

v_{max} (FTIR)cm^{-1}: 2966 (C-H), 1731 (C=O), 1436 (C-H), 1241 (C-O), 1200 (C-O_{ester}), 1165 (C-N), 755 (C-Cl).

HRMS: calcd for $C_{12}H_{18}{}^{35}ClNO_4Na$, *m/z* = 298.0810, found 298.0816

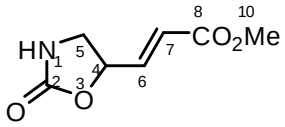
Attempted Preparation of methyl (2*E*)-3-[3-(3-methylbut-2-en-1-yl)-2-oxo-1,3-oxazolidin-5-yl]acrylate (2.19)



(**2.19**)

We were unable to isolate a pure analytical sample of (**2.19)** and decomposition followed.

Preparation of methyl (2*E*)-3-(2-oxo-1,3-oxazolidin-5-yl)acrylate (2.21)



(**2.21**)

This unknown compound was synthesised using a modification of the procedure according to Herweh *et al*.[75].

To a stirring solution of epoxide (**2.16**) (501 mg, 3.9 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added dropwise chlorosulfonyl isocyanate (**2.13**) (553 mg, 3.9 mmol). The resulting solution was left to stir for 4 h. After this time saturated $KI_{(aq)}$ solution (20 mL) was added. The organic components were extracted using CH_2Cl_2 (3 x 15 mL) washed with saturated $NaCl_{(aq)}$ (2 x 15 mL) and water (2 x 15 mL), then dried, ($MgSO_4$) concentrated under reduced pressure and purified via flash chromatography eluting with hexanes/diethyl ether (1:4) to afford the title compound (**2.21**) (110 mg, 17 %) as a brown liquid.

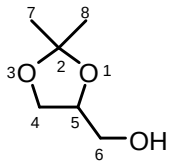
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (dd, *J* = 15.7, 5.5 Hz, 1H, H6), 6.18 (d, *J* = 15.7 Hz, 1H, H7), 5.30 (app. qd, *J* = 7.0, 1.3 Hz, 1H, H4), 4.65 (app. t, *J* = 8.5 Hz, 1H, H5), 4.19 (dd, *J* = 8.5, 7.1 Hz, 1H, H5), 3.75 (s, 3H, H10).

^{13}C NMR (126 MHz, $CDCl_3$): δ 165.3 (C8), 154.1 (C2), 139.7 (C6), 124.5 (C7), 74.6 (C4), 68.5 (C5), 52.0 (C10).

ν_{max} (FTIR)cm^{-1}: 2957 (C-H), 1790 (C=O), 1718 (C=O), 1270 (C-N), 1159 (C-O_{ester}), 1062 (C-O_{ester}).

LRMS (EI^+): *m/z* = **173 (14%)** (Deuterated Form), 149 (67%), 141 (100%), 128 (11%), 100 (60%), 99 (34%), 87 (30%), 69 (37%), 59 (61%), 55 (76%), 42 (44%), 41 (99%), 38 (63%).

Preparation of isopropylidene glycerol (2.27)



(**2.27**)

This known compound was synthesised using a modification of the procedure according to Newman *et al.*[84].

A mixture of glycerol (**2.28**) (100 g, 1.09 mol), acetone (300 mL), pentane (300 mL) and PTSA monohydrate (3 g, 16 mmol) was placed in a single neck 1 L flask fitted with stirrer bar and helices packed 14 inch column topped by a Dean-Stark apparatus and condenser. The mixture was stirred at reflux (temp @ head 31°C) for 35 h (Mixture was homogenous after 13.5 h). The reaction was cooled and neutralised with anhydrous sodium acetate (1.3 g, 16 mmol) then filtered. After removal of solvent the residue was distilled (80 °C 15 mbar) to afford title compound (**2.27**) (135.14 g, 95 %) as a colourless liquid.

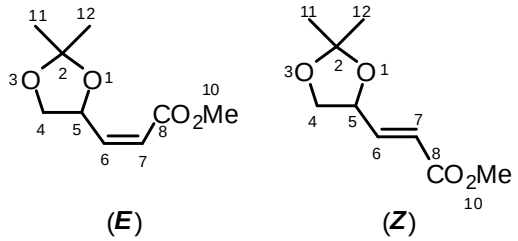
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27 – 4.21 (m, 1H, H5), 4.04 (dd, *J* = 8.4, 7.3 Hz, 1H, H4), 3.80 (dd, *J* = 9.5, 8.4 Hz, 1H, H4), 3.74 (dt, *J* = 11.4, 4.4 Hz, 1H, H6), 3.60 (dt, *J* = 11.4, 5.5 Hz, 1H, H6), 1.83 (s, 1H, OH), 1.45 (s, 3H, H7), 1.38 (s, 3H, H8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 109.4 (C2), 76.1 (C5), 65.7 (C4), 63.0 (C6), 26.7 (C7), 25.0 (C8).

ν_{max} (FTIR)cm^{-1}: 3434 (OH) 2987 (C-H), (2936 (C-H), 1047 (C-$O_{alcohol}$).

HRMS: calcd for $C_6H_{12}O_3Na$, m/z = 155.0679, found 155.0681.

Preparation of methyl (2*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate and methyl (2*Z*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (2.30)



(**2.30**)

These known compounds were synthesised using a modification of the procedure according to Ireland *et al.*[85].

To a stirring solution of $(COCl)_2$ (44.57 g, 349 mmol) in CH_2Cl_2 (750 mL) at -78 °C was added dropwise DMSO (32.0 g, 411 mmol) in CH_2Cl_2 (20 mL) then mixture was left stirring for 20 min before addition of alcohol (**2.27**) (20.93 g, 158 mmol) in CH_2Cl_2 (250 mL) from a dropping funnel. Funnel was rinsed with CH_2Cl_2 (10 mL) and mixture left stirring for additional 30 min. Et_3N (110 mL, 792 mmol) was then placed in dropping funnel, added slowly and left stirring at -78 °C. Following 30 min, the mixture was allowed to warm to -10 °C and (triphenylphosphoranylidene) acetate (79.45 g, 238 mmol) in CH_2Cl_2 (250 mL) was added dropwise before allowing mixture to warm to rt and stir overnight. Following removal of solvent residue was subject to column chromatography eluting with 15% diethyl ether/hexanes to afford title compound (**2.30**) (21.96 g, 74 %) as a pale yellow liquid containing a mixture of *cis*/*trans* isomers. (*E:Z* =1:07) which, was carried forward to next step.

***E* isomer**

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89 (dd, *J* = 15.6, 5.6 Hz, 1H, H6), 6.11 (dd, *J* = 15.6, 1.3 Hz, 1H, H7), 4.66 (td, *J* = 6.8, 6.8 Hz, 1H, H5) 4.18 (dd, *J* = 6.7, 8.2 Hz, 1H, H4), 3.75 (s, 3H, H10), 3.67 (dd, *J* = 7.2, 8.1 Hz, 1H, H4), 1.44 (s, 3H, H11), 1.40 (s, 3H, H12).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.4 (C8), 145.0 (C6), 121.9 (C7), 110.2 (C2), 74.9 (C5), 68.8 (C4), 51.7 (C10), 26.4 (C11), 25.7 (C12).

ν_{max} (FTIR)cm^{-1}: 2987 (C-H), 1719 (C=O), 1438 (C-H), 1200 (C-O), 1180 (C-O), 1154(C-O), 1055.

HRMS: calcd for $C_9H_{14}O_4Na$, *m/z* = 209.0784, found 209.0786.

***Z* isomer**

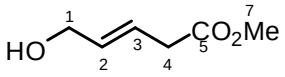
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.37 (dd, *J* = 15.5, 5.6 Hz, 1H, H6), 5.86 (dd, *J* = 15.5, 1.3 Hz, 1H, H7), 5.50 (td, *J* = 6.8, 1.2 Hz, 1H, H5), 4.38 (dd, *J* = 8.3, 6.7 Hz, 1H, H4), 3.72 (s, 3H, H10), 3.62 (dd, *J* = 8.3, 6.7 Hz, 1H, H4), 1.45 (s, 3H, H11), 1.39 (s, 3H, H12).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.0 (C8), 149.5 (C6), 120.3 (C7), 109.7 (C2), 73.45 (C5), 69.3 (C4), 51.5 (C10), 26.5 (C11), 25.4 (C12).

ν_{max} (FTIR)cm^{-1}: 2988 (C-H), 1721 (C=O), 1436 (C-H), 1259 (C-O), 1211 (C-O), 1154 (C-0), 1058.

HRMS: calcd for $C_9H_{14}O_4Na$, *m/z* = 209.0784, found 209.0781.

Preparation of methyl (3E)-5-hydroxy-3-pentenoate (2.25)



(**2.25**)

This known compound was synthesised using a modification of the procedure according to Pak *et al.*[82].

To a solution of (**2.30**) (8.1 g, 44 mmol) in MeOH (225 mL) at -23 °C stirred by a glass stirrer bar was added powdered magnesium (3.2 g, 130 mmol) and carborundum (1 spatula) Following 2 h the mixture was diluted with diethyl ether (225 mL) and filtered through Celite® (500 fine). Following removal of solvent, residue was subject to column chromatography eluting with hexanes/diethyl ether (1:1) to afford the title compound (**2.25**) (3.6 g, 64 %) as a pale yellow liquid.

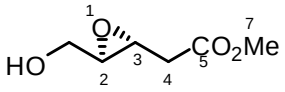
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 – 5.80 (m, 1H, Ha), 5.80 – 5.71 (m 1H, H2), 4.15 (app. t, *J* = 4.7 Hz, 2H, H1), 3.70 (s, 3H, H7), 3.11 (d, *J* = 6.1 Hz, 2H, H4), 1.40 (s, 1H, OH).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.1 (C5), 133.3 (C2), 123.5 (C3), 63.0 (C1), 51.8 (C7), 37.4 (C4).

ν_{max} (FTIR)cm^{-1}: 3420 (OH), 2953 (C-H), 1733 (C=O), 1436 (C-H), 1202 (C-O_{ester}), 1158 (C-O_{ester}), 970 (C-$O_{alcohol}$).

HRMS: calcd for $C_6H_{10}O_3Na$, *m/z* = 153.0522, found 153.0523.

Preparation of methyl 3,4-anhydro-2-depxy-D-threo-pentonate (2.24)



(**2.24**)

This known compound was synthesised using a modification of the procedure according to Sharpless *et al.*[87].

$Ti(^{i}OPr)_4$ (1.86 g, 9.8 mmol) was added to a stirring solution of (+)DIPT (2.29 g, 9.8 mmol) and powdered activated 4Å molecular sieves (2 g) in CH_2Cl_2 (90 mL) at -25°C. (**2.25**) (8.5 g, 65.3 mmol) was added dropwise to this solution followed by dropwise addition of 5M TBHP in CH_2Cl_2 (19.6 mL 98 mmol). Reaction vessel was placed in -25°C freezer for a period of 31 Days. Solution was warmed to 0°C and poured into a stirring solution of ferrous sulfate heptahydrate (3.27 g, 11.8 mmol) in H_2O (18.6 mL). After 10 mins the organic components were extracted using CH_2Cl_2 (3 x 20 mL) combined then dried ($MgSO_4$), concentrated under reduced pressure and purified via column chromatography on neutral silica eluting with hexanes/diethyl ether (1:1) to afford the title compound (**2.24**) (7.59 g, 75 % based on recovered SM) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (d, *J* =12.8 Hz, 1H, H8), 3.71 (s, 3H, H7), 3.66 (d, *J* = 12.8 Hz, 1H, H8), 3.34 - 3.28 (m, 1H, H3), 3.07 – 2.92 (m, 1H, H2), 2.61 (d, *J* = 5.6 Hz, 2H, H4) 2.14 (s, 1H, OH).

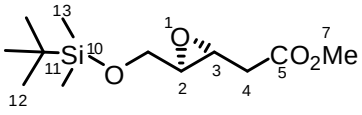
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.7 (C5), 61.2 (C8), 58.1 (C2), 52.0 (C7), 51.3 (C3), 37.0 (C4).

ν_{max} (FTIR)cm^{-1}: 3450 (OH), 2925 (C-H), 1732(C=O), 1438 (C-H), 1259, 1174 (C-O_{ester}), 1158.

HRMS: calcd for $C_6H_{10}O_4Na$, *m/z* = 169.0471, found 169.0472.

$[\alpha]_D^{23}$ = -21.9, (*c* = 1.00, MeOH). No Lit. values found.

Preparation of methyl 3,4-anhydro-5-O[tert-butyl(dimethyl)silyl]-2-depxy-D-threo-pentonate (2.31)



(**2.31**)

This unknown compound was synthesised using a modification of the procedure according to Hon *et al.*[88].

To a stirring solution of (**2.24**) (235 mg, 1.6 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added sequentially imidazole (273 mg, 4.0 mmol), DMAP (20 mg, 0.2 mmol) and TBSCl (363 mg, 2.4 mmol). Following 1 h diethyl ether (10 mL) was added and the reaction quenched with H_2O (10 mL). The organic phase was separated, concentrated under reduced pressure and residue was subject to column chromatography eluting with hexanes/diethyl ether (3:1) to afford the title compound (**2.31**) (402 mg, 96 %) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85 (dd, *J* = 12.0, 3.1 Hz, 1H, H8), 3.73 (s, 3H, H7), 3.69 (dd, *J* = 12.0, 4.6 Hz, 1H, H8), 3.24 – 3.19 (m, 1H, H3), 2.95 – 2.91 (m, 1H, H2), 2.60 (d, *J* = 5.9 Hz, 2H, H4) 0.90 (s, 9H, Hg), 0.07 (d, *J* = 3.6 Hz, 6H, Hh).

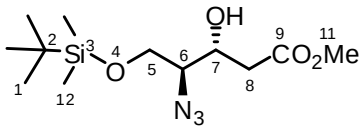
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.7 (C5), 62.9 (C8), 58.4 (C2), 51.9 (C7), 51.4 (C3), 37.2 (C4) 25.8 (C12), 18.3 (C11), -5.4 (C13).

ν_{max} (FTIR)cm^{-1}: 2954 (C-H), 2930 (C-H), 2857 (C-H), 1744(C=O), 1472 (C-H), 1437, 1345, 1255 (Si-CH_3), 1174 (C-O_{ester}), 1107 (Si-OR), 838 (Si-C), 779 (Si-C).

HRMS: calcd for $C_{12}H_{24}O_4SiNa$, *m/z* = 283.1336, found 283.1336.

$[\alpha]_D^{23}$ = -13.0, (*c* = 1.10, MeOH).

Preparation of methyl 4-azido-5-*O*-[*tert*-butyl(dimethyl)silyl]-2,4-dideoxy-L-*erythro*-pentonate (2.32)



(**2.32**)

This unknown compound was synthesised using a modification of the procedure according to Zwanenburg *et al.*[89].

To a stirring solution of (**2.31**) (376 mg, 1.4 mmol) in MeOH/H_2O (10:3, v/v) (3 mL) at rt was added sodium azide (188 mg, 2.9 mmol) and $(NH_4)_2SO_4$ (229 mg, 1.7 mmol) and mixture was heated to reflux. After 48 h the mixture was cooled, diluted with H_2O (10 mL) and diethyl ether (10 mL). Organic components were extracted using diethyl ether (2 x 10 mL), combined, washed with brine (1 x 20 mL) then dried ($MgSO_4$), concentrated under reduced pressure and purified via column chromatography on neutral silica eluting with hexanes/diethyl ether (2:1) to afford the title compound (**2.32**) (144 mg, 47 %) as a yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.07 – 4.01 (m, 1H, H6), 3.95 (dd, *J* = 10.7, 4.1 Hz, 1H, H5), 3.83 (dd, *J* = 10.7, 6.6 Hz, 1H, H5), 3.74 (s, 3H, H11), 3.49 – 3.41 (m, 1H, H7), 2.68 (dd, *J* = 16.6, 3.2 Hz, 1H, H8) 2.55 (dd, *J* = 16.6, 8.7 Hz, 1H, H8), 0.92 (s, 9H, H1), 0.11 (s, 6H, H12).

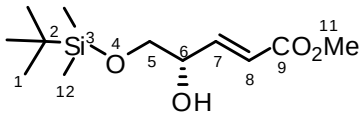
^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9 (C9), 67.8 (C6), 65.7 (C7), 63.6 (C5), 51.9 (C11), 37.6 (C8) 25.7 (C1), 18.1 (C2), -5.6 (C12).

ν_{max} (FTIR)cm^{-1}: 3482 (OH), 2954 (C-H), 2930 (C-H), 2858 (C-H), 2100 (N_3), 1744(C=O), 1464 (C-H), 1438, 1362, 1258 (Si-CH_3), 1173 (C-O_{ester}), 1114 (Si-OR), 838 (Si-C), 779 (Si-C).

LRMS: (ESI^+) $C_{12}H_{24}N_3O_4SiNa$, found 326.1031.

$[\alpha]_D^{23}$ = -24.3, (*c* = 1.75, CH_2Cl_2).

Preparation of methyl (2*E*,4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-hydroxypent-2-enoate (2.34)



(**2.34**)

This known compound was synthesised using a modification of the procedure according to Blum *et al.*[91].

To a stirring solution of (**2.31**) (3.17 g, 12.2 mmol) in acetone/H_2O (1:1, v/v) (36 mL) at rt was added sodium azide (2.77 g, 42.6 mmol) and mixture was heated to reflux. After 56 h the solvent was removed under reduced pressure and residue extracted using CH_2Cl_2 (20 mL). The organic solution was washed with H_2O (2 x 10 mL) then dried (Na_2SO4), concentrated under reduced pressure and purified via column chromatography on neutral silica eluting with hexanes/diethyl ether (5:1) to afford the title compound (**2.34**) (1.61 g, 51 %) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (dd, *J* = 15.8, 4.5 Hz, 1H, H7), 6.11 (d, *J* = 15.8 Hz, 1H, H8), 4.32 (app. s, 1H, H6), 3.71 (s, 3H, H11), 3.70 – 3.71 (m, 1H, H5), 3.48 (dd, *J* = 10.0, 7.1 Hz, 1H, H5) 2.78 (Br. s, 1H, OH), 0.86 (s, 9H, H12), 0.05 (s, 6H, H11).

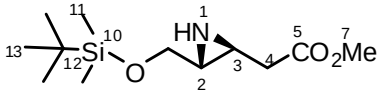
^{13}C NMR (126 MHz, $CDCl_3$): δ 166.7 (C9), 146.2 (C7), 121.3 (C8), 71.3 (C6), 66.2 (C5), 51.5 (C11) 25.8 (C1), 18.2 (C2), -5.5 (C12).

ν_{max} (FTIR)cm^{-1}: 3456 (OH), 2954 (C-H), 2930 (C-H), 2858 (C-H), 1726 (C=O), 1255 (Si-CH_3), 1104 (Si-OR), 834 (Si-C), 776 (Si-C).

HRMS: calcd for $C_{12}H_{26}O_3SiNa$, *m/z* = 260.1676, found 260.1677.

$[\alpha]_D^{24}$ = 0.08, (*c* = 1.85. CH_2Cl_2). No Lit. values found.

Preparation of methyl [(2*S*,3*R*)-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)aziridin-2-yl]acetate (2.29)



(**2.29**)

This unknown compound was synthesised using a modification of the procedure according to Zwanenburg *et al.*[89].

To a stirring solution of (**2.31**) (122 mg, 0.4 mmol) in MeCN (2 mL) at RT was added triphenylphosphine (111 mg). After 10 mins the mixture was heated to reflux. Following 5 h the mixture was cooled and diluted with hexanes/diethyl ether (1:1) (4 mL) before concentrating under reduced pressure. The residue was subject to column chromatography eluting with hexanes/diethyl ether (3:2) to afford the title compound (**2.29**) (81 mg, 79 %) as an orange liquid.

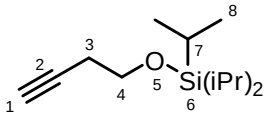
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (d, *J* = 2.4 Hz, 1H, H8), 3.65 (s, 1H, H7), 2.38 (dd, *J* = 16.1, 6.5 Hz, 1H, H4), 2.42 (dd, *J* = 16.1, 6.2 Hz, 1H, H4), 2.18 (app. s, 1H, H3), 1.85 (app. s, 1H, H2) 0.85 (s, 9H, H13), 0.01 (s, 6H, H11).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0 (C5), 61.2 (C8), 51.6 (C7), 38.0 (C4), 37.51 (C2), 28.7 (C3) 25.8 (C13), 18.2 (C12), -5.5 (C11).

ν_{max} (FTIR)cm^{-1}: 2954 (C-H), 2930 (C-H), 2858 (C-H), 1739 (C=O), 1252 (Si-CH_3), 1097 (Si-OR), 834 (Si-C), 776 (Si-C).

HRMS: calcd for $C_{12}H_{24}O_4SiNa$, *m/z* = 283.1336, found 283.1341.

Preparation of (but-3-yn-1-yloxy)(triisopropyl)silane (2.40)



(**2.40**)

This known compound was synthesised using a modification of the procedure according to Razon *et al.*[93].

To a stirring solution of 3-butyn-1-ol (**2.41**) (10.0 g, 143 mmol) and Et_3N (21.7 g, 214 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added dropwise TIPSOTf (45.9 g, 149 mmol). Following 18 h the reaction mixture was washed with saturated $NaHCO_{3(aq)}$ (2 x 150 mL). Organics separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was passed through a silica plug eluting with hexanes/diethyl ether (95:5) to afford the title compound (**2.40**) (32.1 g, 99 %) as a colourless liquid.

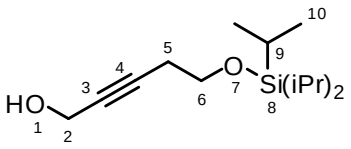
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.80 (t, *J* = 7.3 Hz, 2H, H4), 2.43 (td, *J* = 14.6, 7.3, 2.6 Hz, 2H, H3), 1.94 (t, *J* = 2.6 Hz, 1H, H1), 1.11 – 1.03 (m, 21H, H7/H8).

^{13}C NMR (126 MHz, $CDCl_3$): δ 81.4 (C2), 69.2 (C1), 62.0 (C4), 22.9 (C3), 17.9 (C8), 12.0 (C7).

ν_{max} (FTIR)cm^{-1}: 3315 (C-H_{Alkyne}), 2944 (C-H), 2867 (C-H), 1463, 1114.

HRMS: calcd for $C_{13}H_{26}OSiNa$, *m/z* = 249.1645, found 249.1646.

Preparation of 5-[(triisopropylsilyl)oxy]pent-2-yn-1-ol (2.39)



(**2.39**)

This known compound was synthesised using a modification of the procedure according to Razon *et al.*[93].

To a stirring solution of (**2.40**) (10.0 g, 44.2 mmol) in THF (110 mL) at -78 °C was added dropwise ^{n}BuLi(2.5M) (22.96 mL, 57.4 mmol) Following 25 mins, paraformaldehyde (1.5 g, 48.6 mmol) was added in one portion and mixture left stirring for 6 h. Reaction quenched with H_2O (100 mL). Organics separated and aqueous phase extracted with diethylether (3 x 50 mL) and organic phases combined, dried (Na_2SO_4) and concentrated under reduced pressure. Residue was subject to column chromatography eluting with hexanes/diethyl ether (93:7 – 85:15) to afford the title compound (**2.39**) (9.78 g, 92 %) as a colourless liquid.

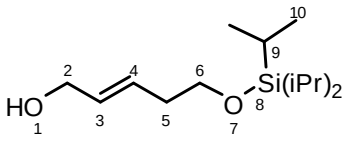
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.22 (s, 1H, H2), 3.79 (t, *J* = 7.5 Hz, 1H, H5), 2.45 (t, *J* = 7.3 Hz, 1H, H6), 1.73 (s, 1H, OH), 1.11 – 1.03 (m, 21H, H9/H10).

^{13}C NMR (126 MHz, $CDCl_3$): δ 83.1 (C4), 79.5 (C3), 62.1 (C5), 51.0 (C2), 23.1 (C6), 17.9 (C9), 11.9 (C10).

ν_{max} (FTIR)cm^{-1}: 3336 (O-H), 2942 (C-H), 2866 (C-H), 1463, 1107.

HRMS: calcd for $C_{14}H_{28}O_2SiNa$, *m/z* = 279.1751, found 279.1747.

Preparation of (2*E*)-5-[(triisopropylsilyl)oxy]pent-2-en-1-ol (2.38)



(**2.38**)

This known compound was synthesised using a modification of the procedure according to Razon *et al.*[93].

(**2.39**) was added dropwise to a stirring solution of LAH (3.01 g, 80.5 mmol) in THF (250 mL) at -10 °C The mixture was warmed to RT and left overnight. The mixture was cooled to -5 °C and cautiously quenched with 5% $NaOH_{(aq)}$ (200 mL). H_2O (200 mL) was added and the phases separated. Aqueous phase was extracted with diethylether (3 x 200 mL) and and organic phases combined, dried (Na_2SO_4) and concentrated under reduced pressure. Residue was subject to column chromatography eluting with hexanes/diethyl ether (4:1) to afford the title compound (**2.38**) (19.41 g, 98 %) as a colourless liquid.

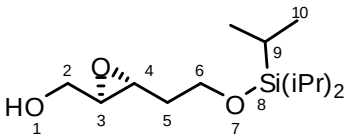
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71 (m, 1H, H4), 5.70 (m, 1H, H3), 4.07 (d, *J* = 4.1 Hz, 2H, H2), 3.70 (t, *J* = 6.7 Hz, 2H, H6), 2.31 (app. t, *J* = 6.7 Hz, 2H, H5), 1.48 (s, 1H, OH), 1.09 – 1.02 (m, 21H, H9/H10).

^{13}C NMR (126 MHz, $CDCl_3$): δ 130.8 (C3), 129.6 (C4), 63.7 (C2), 63.0 (C6), 36.0 (C5), 18.0 (C9), 12.0 (C10).

ν_{max} (FTIR)cm^{-1}: 3337 (O-H), 2943 (C-H), 2866 (C-H), 1463, 1105.

HRMS: calcd for $C_{14}H_{30}O_2SiNa$, *m/z* = 281.1907, found 281.1904.

Preparation of 3,4-anhydro-2-deoxy-1-*O*-(triisopropylsilyl)-L-*threo*-pentitol (2.37)



(**2.37**)

This novel compound was synthesised using a modification of the procedure according to Sharpless *et al.*[87].

$Ti(^iOPr)_4$ (2.09 g, 7.35 mmol) was added to a stirring solution of (+)DIPT (2.58 g, 11.0 mmol) and powdered activated 4Å molecular sieves (3.0 g) in CH_2Cl_2 (100 mL) at -25 °C. (**2.38**) (19.01 g, 73.5 mmol) was added dropwise to this solution followed by dropwise addition of 5M TBHP in CH_2Cl_2 (22 mL, 110 mmol). Reaction vessel was placed in -25 °C freezer overnight. Solution was warmed to 0 °C and quenched with 40 mL of water. After stirring for an additional hour 30% NaOH saturated with NaCl in water (9.5 mL) was added and mixture stirred vigorously for 30 mins before filtering through glass paper and separation of organic phase. The organic components were extracted using CH_2Cl_2 (3 x 100 mL) combined then dried (Na_2SO_4), concentrated under reduced pressure and purified via column chromatography on neutral silica eluting with hexanes/diethyl ether (2:1) to afford the title compound (**2.37**) (13.56 g, 67 %) as a colourless oil.

General Preparation and Analysis of Moshers Esters.

DMAP (18 mg 0.15 mmol) Et_3N (100 µL) were dissolved in stirring CH_2Cl_2 (0.5 mL) The epoxide (either neat or as an aliquot of a crude epoxidation reaction mixture) was added and immediately, (+)-a-methoxy-a-(trifluoromethy1)phenylacetyl chloride (MTPA chloride) (30 µL) was added. The solution became warm and turned orange. Following 5 min reactions were quenched by addition of 3-(dimethylamino)propylamine (40-60 µL) and concentrated, and the residue was passed through a short plug of silica gel in order to remove polar impurities (20% EtOAc/hexane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (ddd, *J* = 12.5, 5.6, 2.4 Hz, 1H, H2), 3.83 (t, *J* = 6.2 Hz, 2H, H6), 3.66 – 3.56 (ddd, *J* = 12.0, 7.2, 4.7 Hz, 1H, H2), 3.11 (td, *J* = 5.9, 2.3 Hz, 1H, H4), 2.98 (dt, *J* = 4.6, 2.4 Hz, 1H, H3), 1.90 (t, *J* = 6.3 Hz, 1H, OH), 1.85 – 1.72 (m, 2H, H5), 1.14 – 0.98 (m, 21H, H9/H10).

^{13}C NMR (126 MHz, $CDCl_3$): δ 61.8 (C2), 60.1 (C6), 58.6 (C3), 53.8 (C4), 35.1 (C5), 18.0 (C9), 11.9 (C10).

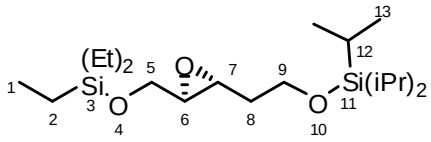
ν_{max} (FTIR)cm^{-1}: 3435 (O-H), 2944 (C-H), 2867 (C-H), 1464, 1107.

HRMS: calcd for $C_{14}H_{30}O_3SiNa$, *m/z* = 297.1856, found 297.1858.

$[\alpha]_D^{24}$ = -27.1 (*c* = 1.70, CH_2Cl_2).

Enantiomeric excess = 64%. See Appendix for ^{1}H-NMR spectra of Moshers esters.

Preparation of 3,4-anhydro-2-deoxy-5-*O*-(triethylsilyl)-1-*O*-(triisopropylsilyl)-L-*threo*-pentitol (2.43)



(**2.43**)

This novel compound was synthesised using a modification of the procedure according to Corey *et al.*[92].

To a stirring solution of (**2.37**) (200 g, 72.3 mmol) and imidazole (14.86 g, 218.6 mmol) in CH_2Cl_2 (275 mL) at rt was added dropwise TESCl (13.88 g, 87.4 mmol). Following 1 h, reaction quenched with brine (150 mL). The organics were extracted with CH_2Cl_2 (3 x 150 mL), combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subject to column chromatography eluting with hexanes/diethyl ether (98:2) to afford the title compound (**2.43**) (27.44 g, 97 %) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 – 3.83 (m, 2H, H9), 3.83 – 3.81 (m, 1H, H5), 3.67 – 3.61 (dd, *J* = 11.8, 4.9 Hz, 1H, H5), 3.01 (m, 1H, H7), 2.91 (m, 1H, H6), 1.92 – 1.78 (m, 1H, H8), 1.78 – 1.67 (m, 1H, H8), 1.16 – 1.00 (m, 21H, H12/H13), 0.96 (t, *J* = 8.0 Hz, 9H, H1i), 0.62 (q, J = 8.0 Hz, 6H, H2).

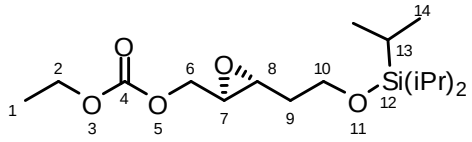
^{13}C NMR (126 MHz, $CDCl_3$): δ 63.3 (C5), 60.2 (C9), 58.8 (C6), 53.8 (C7), 35.4 (C8), 17.9 (C12), 11.9 (C13), 6.6 (C1), 4.4 (C2).

ν_{max} (FTIR)cm^{-1}: 2943 (C-H), 2867 (C-H), 1462, 1100 (C-O).

HRMS: calcd for $C_{20}H_{44}O_3Si_2Na$, *m/z* = 411.2721, found 411.2719.

$[\alpha]_D^{24}$ = -10.1 (*c* = 1.10, CH_2Cl_2).

Preparation of 3,4-anhydro-2-deoxy-5-*O*-(ethoxycarbonyl)-1-*O*-(triisopropylsilyl)-L-*threo*-pentitol (2.44)



(**2.44**)

This novel compound was synthesised using a modification of the procedure according to Guo *et al.*[96].

To a stirring solution of (**2.37**) (1.0 g, 3.65 mmol), DMAP (76 mg, 0.62 mmol) and pyridine (1.15 g, 14.6 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added dropwise ethyl chloroformate (1.58 g, 14.6 mmol). After 3 h a precipitate formed and saturated $CuSO_{4(aq)}$ (30 mL) was added. The aqueous mixture was extracted with diethyl ether (3 x 30 mL), the organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subject to column chromatography eluting with hexanes/diethyl ether (9:1) to afford the title compound (**2.44**) (1.2 g, 95 %) as a yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.36 (dd, *J* = 12.0, 3.2 Hz, 1H, H6), 4.20 (q, *J* = 7.1 Hz, 2H, H2), 4.04 (dd, *J* = 12.0, 6.0 Hz, 1H, H6), 3.83 (t, *J* = 6.2 Hz, 2H, H10), 3.07 – 3.04 (m, 1H, H7), 3.04 – 3.01 (m, 1H, H8), 1.88 – 1.79 (m, 1H, H9), 1.79 – 1.70 (m, 1H, H9), 1.30 (t, *J* = 7.3 Hz, 3H, H1,) 1.13 – 1.00 (m, 42H, H13/H14)

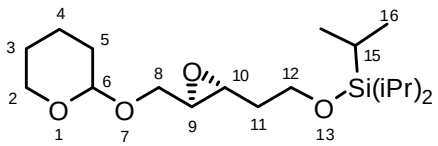
^{13}C NMR (126 MHz, $CDCl_3$): δ 154.9 (C4), 67.8 (C6), 64.2 (C2), 60.0 (C10), 55.1 (C7), 54.2 (C8), 35.1 (C9), 17.9 (C14), 14.2 (C1), 11.9 (C13).

ν_{max} (FTIR)cm^{-1}: 2944 (C-H), 2867 (C-H), 1748 (C-O), 1464, 1250 (C-O).

HRMS: calcd for $C_{17}H_{34}O_5SiNa$, *m/z* = 369.2068, found 369.2072.

$[\alpha]_D^{24}$ = -24.6 (*c* = 1.80, CH_2Cl_2).

Preparation of 3,4-anhydro-2-deoxy-5-*O*-(tetrahydro-2*H*-pyran-2-yl)-1-*O*-(triisopropylsilyl)-L-*threo*-pentitol (2.45)



(**2.45**)

This novel compound was synthesised using a modification of the procedure according to Miyashita *et al.*[97].

To a stirring solution of (**2.37**) (13.25 g, 48.3 mmol), and DHP (6.09 g, 72.4 mmol) in CH_2Cl_2 (350 mL) at rt was added PPTS (1.15 g, 4.8 mmol). After 36 h diethyl ether (150 mL) and 50% $brine_{(aq)}$ (300 mL) was added. The organic phase was separated and organics extracted with CH_2Cl_2 (100 mL), combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subject to column chromatography eluting with hexanes/diethyl ether (4:1) to afford the title compound (**2.45**) (16.10 g, 93 %) as a yellow oil consisting of a mixture of diastereomers.

^{1}H NMR and ^{13}C NMR values have been characterised by arbitrary assignment of peaks due to recognition of diastereomers caused by the chirality of THP group. Compounds confirmed by associated Mass and IR data.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.70 – 4.57 (m, 2H, H6), 3.95 – 3.89 (m, 1H, H12(dia2)), 3.84-3.89 (m, 2H, H2), 3.83 – 3.77 (m, 2H, H9), 3.76 – 3.64 (m, 2H, H12), 3.53 – 3.45 (m, 2H, H2(dia2)), 3.44-3.36 (m, 1H, H12(dia2)), 3.09-3.02 (m, 2H, H8), 3.02 – 2.99 (m, 2H, H10), 2.98-2.92 (m, 2H, H8(dia2)), 1.89 – 1.77 (m, 4H, H11), 1.77 – 1.65 (m, 4H, H3), 1.65 – 1.54 (m, 4H, H5), 1.55-1.45 (m, 4H, H4), 1.08 – 1.04 (m, 42H, H15/H16).

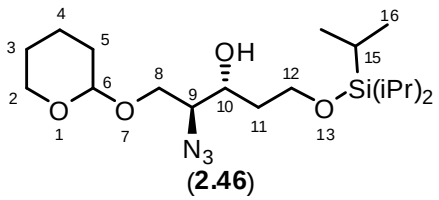
^{13}C NMR (126 MHz, $CDCl_3$): δ 98.8 (C6), 98.5 (C6), 67.9 (C12), 66.8 (C12(dia2)), 62.0 (C2), 61.9 (C2(dia2)), 60.2 (C9), 57.3 (C10(dia2)), 56.9 (C10), 53.8 (C8), 35.3 (C3), 30.5 (C5(dia2)), 30.4 (C5), 25.4 (C4), 19.2 (C11(dia2)), 19.1 (C11), 18.0 (C16), 11.9 (C15).

ν_{max} (FTIR)cm^{-1}: 2942 (C-H), 2865 (C-H), 1463, 1106 (C-O), 1032 (C-O).

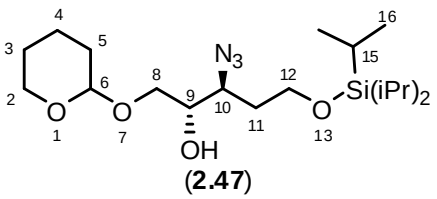
HRMS: calcd for $C_{19}H_{38}O_4SiNa$, *m/z* = 381.2432, found 381.2433.

$[\alpha]_D^{23}$ = -29.2 (*c* = 2.00), CH_2Cl_2).

Preparation of 4-azido-2,4-dideoxy-5-*O*-(tetrahydro-2*H*-pyran-2-yl)-1-*O*-(triisopropylsilyl)-D-*erythro*-pentitol) (2.46) and 3-azido-3,4-dideoxy-1-*O*-(tetrahydro-2*H*-pyran-2-yl)-5-*O*-(triisopropylsilyl)-D-*erythro*-pentitol (2.47)



(**2.46**)



(**2.47**)

These novel compunds were synthesised using a modification of the procedure according to Zwanenburg *et al.*[89].

To a stirring solution of (**2.45**) (3.00 g, 8.4 mmol) in MeOH/H_2O (10:3, v/v) (39 mL) at rt was added sodium azide (1.09 g, 16.79 mmol) and $(NH_4)_2SO_4$ (1.33 mg, 1.7 mmol) and mixture was heated to reflux. After 54 h the mixture was cooled, diluted with H_2O (30 mL) and diethyl ether (50 mL). The organic components were extracted using diethyl ether (2 x 50 mL) combined, washed with brine (1 x 50 mL) then dried (Na_2SO_4), concentrated under reduced pressure and purified via column chromatography on neutral silica eluting with hexanes/diethyl ether (9:1-4:1) to afford an inseparable mixture of the title compounds (**2.46**) and (**2.47**) (2.62 g, 78 %) as a yellow oil.

^{1}H NMR and ^{13}C NMR values have been characterised by arbitrary assignment of peaks due to recognition of diastereomers caused by the chirality of THP group. Compounds confirmed by associated Mass and IR data.

(2.46)

^{1}H NMR (500 MHz, $CDCl_3$): δ δ 4.60-4.59 (m, 1H, H6(dia2)), 4.59-4.55 (m, 1H, H6), 3.95 – 3.91 (m, 2H, H9(dia2)), 3.91 – 3.85 (m, 4H, H8), 3.85 – 3.82 (m, 2H, H2), 3.81 – 3.80 (m, 2H, H12(dia2)), 3.79 – 3.73 (m, 2H, H10), 3.73-3.71 (m, 2H, H2(dia2)), 3.71 – 3.67 (m, 2H, H12), 3.59 – 3.51 (m, 1H, H9), 2.05 – 1.96 (m, 1H, H11(dia2)), 1.96 – 1.87 (m, 1H, H11(dia2)), 1.87 –1.77 (m, 2H, H4), 1.77 – 1.63 (m, 4H, H5), 1.62 – 1.57 (m, 2H, H11), 1.57 - 1.55 (m, 4H, H3), 1.55 - 1.49 (m, 2H, H4(dia2)), 1.14 – 1.01 (m, 42H, H16/H16)

^{13}C NMR (126 MHz, $CDCl_3$): δ 100.42 (C6), 100.10 (C6(dia2)), 72.92 (C12(dia2)), 72.71 (C12), 70.15 (C2(dia2)), 69.75 (C2) 63.34 (C9), 63.12 (C9(dia2)), 60.88 (C10(dia2)), 60.75 (C10), 59.73 (C8), 59.69 (C8(dia2)), 33.54 (C11), 33.42 (C11(dia2)), 30.68 (C5), 25.18 (C3), 19.97 (C4), 19.78 (C4(dia2)), 17.97 (C16), 11.94 (C15).

ν_{max} (FTIR)cm^{-1}: 3407 (OH), 2942 (C-H), 2866 (C-H), 2100 (N_3), 1463 (C-H), 1258 (Si-CH_3), 1102 (C-O_{ester}), 1064, 1032, 881 (Si-C), 679 (Si-C).

HRMS: calcd for $C_{19}H_{39}O_4SiNa$, *m/z* = 424.2602, found 424.2609.

$[\alpha]_D^{22}$ = 11.5 (*c* = 1.40, CH_2Cl_2).

(**2.47**)

^{1}H NMR (500 MHz, $CDCl_3$): δ δ 4.69 – 4.64 (m, 2H, H6), 4.12 – 4.05 (m, 1H, H12), 4.05 – 3.99 (m, 2H, H8), 3.94-3.93 (m, 1H, H12), 3.92 – 3.89 (m, 2H, H8(dia2)), 3.89-3.84 (m, 4H, H2), 3.77-3.73 (m, 1H, H12), 3.61 – 3.57 (m, 1H, H12), 3.57 – 3.54 (m, 1H, H10(dia2)), 3.54 – 3.51 (m, 2H, H9), 3.51-3.49 (m, 1H, H10), 1.91 – 1.79 (m, 4H, H11), 1.79 – 1.66 (m, 4H, H5), 1.67 – 1.56 (m, 4H, H3), 1.55 – 1.46 (m, 4H, H4), 1.10 – 1.05 (m, 42H, H15/H16).

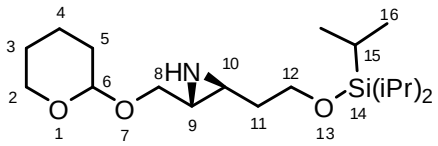
^{13}C NMR (126 MHz, $CDCl_3$): δ 99.4 (C6(dia2)), 98.5 (C6), 71.8 (C2(dia2)), 71.4 (C2), 67.7 (C12(dia2)), 67.2 (C12) 65.5 (C10(dia2)), 65.3 (C10), 63.0 (C8(dia2)), 62.8 (C8), 62.1 (C9(dia2)), 61.8 (C9), 34.8 (C11(dia2)), 34.6 (C11), 30.3 (C5), 25.4 (C3), 19.1 (C4(dia2)), 18.9 (C4), 17.9 (C16), 11.7 (C15).

ν_{max} (FTIR)cm^{-1}: 3474 (OH), 2942 (C-H), 2866 (C-H), 2096 (N_3), 1463 (C-H), 1262 (Si-CH_3), 1122 (C-O_{ester}), 1065, 1032, 881 (Si-C), 679 (Si-C).

HRMS: calcd for $C_{19}H_{39}O_4SiNa$, *m/z* = 424.2602, found 424.2606.

$[\alpha]_D^{24}$ = -9.3 (*c* = 2.00, CH_2Cl_2).

Preparation of ((2*R*,3*S*)-2-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]-3-{2-[(triisopropylsilyl)oxy]ethyl}aziridine (2.42)



(**2.42**)

This novel compound was synthesised using a modification of the procedure according to Zwanenburg *et al.*[89].

To a stirring solution of (**2.46**) and (**2.47**) (9.00 g, 22.4 mmol) in MeCN (120 mL) at rt was added triphenylphosphine (6.17 g 23.5 mmol). After 10 mins the mixture was heated to reflux. Following 4 h the mixture was cooled, diluted with diethyl ether (100 mL) and placed in freezer overnight. The precipitate was filtered off and filtrate concentrated under reduced pressure before addition of hexanes (50 mL) and precipitate again filtered before concentrating under reduced pressure. The residue was subjected to column chromatography eluting with hexanes/diethyl ether (1:3) to afford the title compound (**2.42**) (7.70 g, 96 %) as yellow oil.

^{1}H NMR and ^{13}C NMR values have been characterised by arbitrary assignment of peaks due to recognition of diastereomers caused by the chirality of THP group. Compounds confirmed by associated Mass and IR data.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.62 – 4.54 (m, 2H, H6), 3.84 – 3.80 (m, 2H, H8(dia2)), 3.78 (t, *J* = 6.1 Hz, 4H H2), 3.60 (m, 2H, H8), 3.46 (app. t, *J* = 5.5 Hz, 2H, H12), 3.43 (app. t, *J* = 5.5 Hz, 2H, H12) 3.34 (s, 2H, H17), 1.93 (m, 1H, H9), 1.82 – 1.73 (m, 2H, H11(dia2)), 1.71 – 1.66 (m, 1H, H10), 1.66 – 1.62 (m, 4H, H5), 1.56-1.50 (m, 4H, H4), 1.50 – 1.47 (m, 4H, H3), 1.47 – 1.42 (m, 2H, H11(dia2)), 1.03- 1.00 (m, 21H, H15/H16).

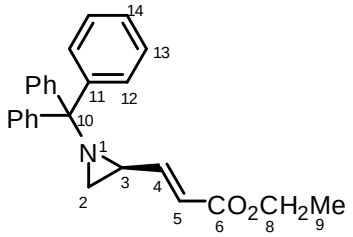
^{13}C NMR (126 MHz, $CDCl_3$): δ 98.8 (C6(dia2)), 98.4 (C6), 68.7 (C8(dia2)), 62.2 (C12), 61.9 (C8), 61.6 (C2) 61.6 (C2(dia2)), 36.8 (C10), 36.0 (C9), 30.5 (C5), 30.4 (C4), 25.4 (C3), 19.4 (C11(dia 2), 19.2 (C11), 17.9 (C15), 11.9 (C16).

ν_{max} (FTIR)cm^{-1}: 3292 (N-H), (2942 (C-H), 2866 (C-H), 1463, 1200 (Si-CH_3), 1119 (Si-OR), 882 (Si-C).

HRMS: calcd for $C_{19}H_{40}O_3SiNa$, *m/z* = 358.2772, found 358.2769.

$[\alpha]_D^{24}$ = 23.3 (*c* = 1.95 in CH_2Cl_2).

Preparation of ethyl (2*E*)-3-[(2*S*)-1-tritylaziridin-2-yl]acrylate (2.52)



(**2.52**)

This novel compound was synthesised using a modification of the procedure according to Fujii *et al.*[100].

To a stirring solution of methyl (S)-(-)-1-tritylaziridine-2-carboxylate (**2.53**) (1.0 g, 2.91 mmol) in CH_2Cl_2 (10 mL) at -78°C was added dropwise DIBAL-H (1M in diethyl ether) (3.2 mL, 3.20 mmol). Following 1 h solution was warmed to -10°C and saturated aqueous NH_4Cl (1.8 mL) was added followed by cannular addition of the sodium salt of triethyl phosphonoacetate (1.96 g 8.74 mmol) in THF (15 m L). Following 16 h at rt, liquid decanted off solid and solvent removed under reduced pressure. The residue was subject to column chromatography eluting with diethyl ether/hexanes (5:95) to afford the title compound (**2.52**) (965 mg, 86 %) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.18 (m 15H, H12/H13/H14$_{(aromatics)}$) 6.95 (dd, *J* = 8.1, 15.57 1H, H4), 6.04 (d, *J* = 15.57 Hz, 1H, H5), 4.22 (q, *J* = 14.33, 7.2 Hz, 2H, H8), 1.92 (app. d, *J* = 2.45 Hz, 1H, H2), 1.83 (t, *J* = 6.83 Hz, 1H, H3), 1.50 (app. d, *J* = 6.83 Hz, 1H, H2), 1.31 (t, *J* = 7.1 Hz, 3H, H9).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.3 (C10), 149.9 (C4), 144.0 (C6), 129.4 (C12), 127.5 (C13), 126.8 (C14), 122.0 (C5), 74.5 (C11), 60.3 (C8), 33.1 (C2), 30.7 (C3), 14.2 (C9).

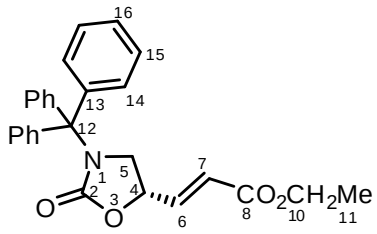
ν_{max} (FTIR)cm^{-1}: 3057 (C-H), 2982 (C-H), 2866 (C-H), 1714 (C=O).

HRMS: calcd for $C_{26}H_{25}NO_2Na$, *m/z* = 406.1778, found 406.1773.

$[\alpha]_D^{22}$ = -138.9 (*c* = 1.20, $CHCl_3$).

Mp. 38.5-41.1°C.

Preparation of ethyl (2*E*)-3-[(5*S*)-2-oxo-3-trityl-1,3-oxazolidin-5-yl]acrylate (2.56)



(**2.56**)

This novel compound was synthesised using a modification of the procedure according to Pinhas *et al.*[101].

Aziridine (**2.52**) (387 mg, 1.01 mmol) was dissolved in stirring THF (15 mL) in a thick walled screw capped vial (30 mL). NaI (151 mg, 1.01 mmol) was added and the whole cooled to -78°C. Solid CO_2 (8.0 g, 450 mmol) was added, the cap sealed and the vial placed behind a blast shield. After 2 days at rt the vial was again cooled to -78°C and the cap was carefully removed. The solution was washed with saturated aqueous sodium thiosulphate and organics extracted with diethyl ether (3 x 20 mL) combined, dried (Na_2SO_4) and filtered before concentrating under reduced pressure. The residue was subject to column chromatography eluting with hexanes/diethyl ether (3:2) to afford the title compound (**2.56**) (314 mg, 73 %) as gummy yellow solid (attempts at recrystallisation of highly insoluble material caused decomposition to black tar).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.09 (m, 15H, H14/H15/H16$_{(aromatics)}$) 6.85 (app. d, *J* = 15.3, Hz, 1H, H6), 6.12 (d, *J* = 15.6 Hz, 1H, H7), 4.34 (app. s br, 1H, H4), 4.27 – 4.12 (m, 2H, H10), 2.45 (dd, *J* = 8.0, 3.73 Hz, 1H, H5), 2.32 (dd, *J* = 8.0, 3.73 Hz, 1H, H5), 1.29 (app. d, *J* = 3.6 Hz, 3H, H11).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.3 (C8), 147.8 (C6), 145.5 (C2), 128.6 (C14), 128.0 (C15), 126.6 (C16), 121.3 (C7), 108.4 (C13), 70.6 (C4), 60.5 (C10), 48.8 (C5), 14.2 (C11).

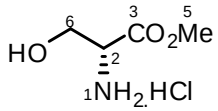
ν_{max} (FTIR)cm^{-1}: 3057 (C-H), (2926 (C-H), 2854 (C-H), 1704 (C=O).

LRMS (EI^{+}): *m/z* = 324 (78%), 243 (100%), 165 (17%).

$[\alpha]_D^{22}$ = 0.4 (*c* = 1.00, $CHCl_3$).

Mp. 37.9- 39.2 °C.

Preparation of D-serine methyl ester hydrochloride (2.62)



(**2.62**)

This known compound was synthesised using a modification of the procedure according to nudelman *et al.*[102].

Acetyl chloride (50 g, 319 mmol) was added dropwise to stirring MeOH (350 mL) at -5 °C. D-Serine (25 g, 238 mmol) was added in one portion and the mixture was heated to reflux. Following 3 h, the solvent was removed under vacuum and solid recrystallised from MeOH (45 mL) to yield the title compound (**2.62**) (33.11 g, 89 %) as a white solid.

^{1}H NMR (500 MHz, DMSO) δ 8.64 (s, 3H, H1), 5.86 – 5.29 (brd. s , 1H, OH), 4.14 – 3.96 (m, 1H, H2), 3.82 (d, *J* = 3.3 Hz, 2H, H6), 3.72 (s, 3H, H5).

^{13}C NMR (126 MHz, DMSO) δ 168.9 (C3), 59.9 (C6), 54.9 (C2), 53.2 (C5).

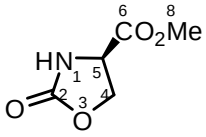
ν_{max} (FTIR)cm^{-1}: 3343 (OH), 2918 (C-H), 1745 (C-0), 1038 (C-O$_{alcohol}$).

HRMS: calcd for $C_4H_{10}NO_3Na$, m/z = 120.0655, found 120.0658.

$[\alpha]_D^{23}$ = -4.1 (c = 1.05, MeOH). Lit. $[\alpha]_D^{20}$ = -4.0[127]

Mp. 163-165°C. Lit. Mp = 164-166°C[127].

Preparation of methyl (4*S*)-2-oxo-1,3-oxazolidine-4-carboxylate (2.61)



(**2.61**)

This known compound was synthesised using a modification of the procedure according to Nudelman *et al.*[103].

Et_3N (97.56 g, 964.1 mmol) was added to a stirring solution of (**2.62**) (50.0 g, 321.4 mmol) in CH_2Cl_2 (600 mL) at 0°C. Following 10 m a solution of triphosgene (47.68 g, 160.7 mmol) in CH_2Cl_2 (300 mL) was added dropwise over 2 h. Following 24 h at rt, the mixture was cooled to -78°C to precipitate any salts before filtering and removal of solvent under reduced pressure. The residue was purified on a plug of silica washed with AcOEt (300 mL) to provide title compound (**2.61**) (46.60 g, 100 %) as an orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.19 (s, 1H, H1), 4.61 (app. t, *J* = 9.2 Hz, 1H, H4), 4.53 (dd, *J* = 9.0, 4.6 Hz, 1H, H4), 4.43 (dd, *J* = 9.2, 4.6 Hz, 1H, H5), 3.82 (s, 3H, H8).

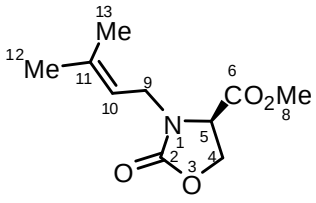
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4 (C2), 158.8 (C6), 66.7 (C4), 53.71 (C5), 53.1 (C8).

ν_{max} (FTIR)cm^{-1}: 3296 (OH) 2959 (C-H), 1727 (C=O), 1209.

HRMS: calcd for $C_5H_7NO_4Na$, m/z = 168.0267, found 168.0268.

$[\alpha]_D^{22}$ = -18.2 (*c* = 1.05, CH_2Cl_2). Lit. $[\alpha]_D^{25}$ = -18.6[128].

Preparation of methyl (4*S*)-3-(3-methylbut-2-en-1-yl)-2-oxo-1,3-oxazolidine-4-carboxylate (2.60)



(**2.60**)

This novel compound was synthesised using a modification of the procedure according to Nudelman *et al.*[104].

Oxazolidinone (**2.61**) (360 mg, 2.48 mmol) was added dropwise to a stirring suspension of NaH (65 mg 2.73 mmol) in 4:1 THF/DMF (5 mL). Upon complete dissolution of solids, 3,3-dimethyl allyl bromide (506 mg 3.23 mmol) was added dropwise. Following 16 h, water (5 mL) was added and organics extracted with diethyl ether (3 x 30 mL), combined, dried (Na_2SO_4) and solvent removed under reduced pressure. The residue was subject to column chromatography eluting with hexanes/ethyl acetate (3:1) to afford the title compound (**2.60**) (410 mg, 78 %) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.13 (t, J = 7.4 Hz, 1H, H10), 4.50 – 4.36 (m, 1H, H4), 4.35 – 4.25 (m, 2H, H4), 4.13 (dd, J = 14.8, 6.2 Hz, 1H, H9), 3.3 (dd, J = 14.8, 8.8 Hz, 1H, H9), 3.78 (s, 3H, H8), 1.76 (s, 3H, H12), 1.65 (s, 3H, H13).

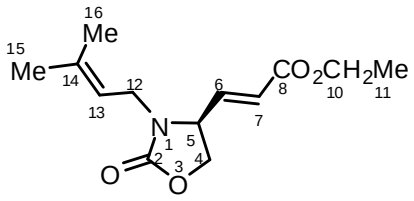
^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3 (C6), 157.4 (C2), 139.0 (C11), 117.3 (C10), 64.3 (C4), 56.2 (C5), 52.8 (C8), 40.9 (C9), 25.7 (C12), 17.7 (C13).

ν_{max} (FTIR)cm^{-1}: 2919 (C-H), 1739 (C=O), 1207 (C-O), 1173.

HRMS: calcd for $C_{10}H_{15}NO_4Na$, m/z = 236.0893, found 236.0893.

$[\alpha]_D^{24}$ = +21.1 (c = 1.00, CH_2Cl_2).

Preparation of ethyl (2*E*)-3-[(4*R*)-3-(3-methylbut-2-en-1-yl)-2-oxo-1,3-oxazolidin-4-yl]acrylate (2.1)



(**2.1**)

This novel compound was synthesised using a modification of the procedure according to Nudelman *et al.*[104].

To a stirring solution of methyl ester (**2.60**) (321 mg, 1.51 mmol) in CH_2Cl_2 (5 mL) at -78°C was added dropwise DIBAL-H(1M in diethyl ether) (2.4 mL, 2.4 mmol). Following 1 h solution was warmed to -10°C and sat. $NH_4Cl_{(aq)}$ (3.0 mL) was added followed by cannular addition of ethyl (triphenylphosphoranylidene)acetate (1.57 g 4.52 mmol) in CH_2Cl_2 (5 mL) Following 16 h at rt, liquid was decanted off solid and solvent removed under reduced pressure. The residue was subject to column chromatography eluting with hexanes/ethyl acetate (4:1) to afford the title compound (**2.1**) (318 mg, 83 %) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 (dd, *J* = 8.5, 15.7 Hz,1H, H6), 6.00 (d, *J* = 15.6 Hz, 1H, H7), 5.13 (t, *J* = 7.3 Hz, 1H, H13), 4.43 (app. t, *J* = 8.3 Hz, 1H, H4), 4.34 (app. dd, *J* = 15.3, 8.4 Hz, 1H, H5), 4.23 (q, *J* = 7.1 Hz, 2H, H10), 4.03 (dd, *J* = 15.0, 6.2 Hz, 1H, H12), 3.99 (dd, *J* = 8.4, 6.2 Hz, 1H, H4), 3.60 (dd, *J* = 15.1, 8.4 Hz, 1H, H12), 1.73 (s, 3H, H15), 1.63 (s, 3H, H16), 1.31 (t, *J* = 7.2 Hz, 3H, H11).

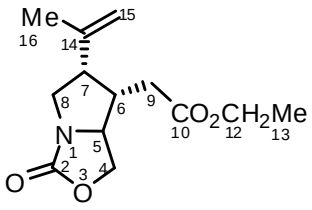
^{13}C NMR (126 MHz, $CDCl_3$): δ 165.0 (C8), 157.6 (C2), 143.0 (C7), 138.1 (C14), 125.7 (C6), 117.7 (C13), 66.2 (C4), 61.0 (C10), 56.3 (C5), 40.3 (C12), 25.7 (C15), 18.0 (C16), 14.1 (C11).

ν_{max} (FTIR)cm^{-1}: 2979 (C-H), 2911 (C-H), 1748 (C=O), 1717 (C=O), 1263, 1175 (C-O), 1055.

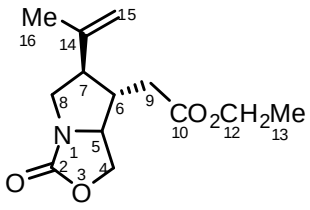
HRMS: calcd for $C_{13}H_{19}NO_4Na$, m/z = 276.1206, found 276.1215.

$[\alpha]_D^{24}$ = +36.7 (c = 1.10, CH_2Cl_2).

Preparation of ethyl [(6*S*,7*S*)-6-isopropenyl-3-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-7-yl]acetate (2.65) and ethyl [(6*R*,7*S*)-6-isopropenyl-3-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-7-yl]acetate (2.69)



(**2.65**)



(**2.69**)

Ene precursor (**2.1**) (1 g 3.95 mmol) was dissolved in *N*,*N*-diethylaniline (20 mL) in a thick walled microwave vial (35 mL). The vial was placed in the microwave at 200 °C for 4 h. The crude solution was subject to column chromatography eluting with hexanes/ethyl acetate (5:1) to afford a semi-separable 7:1 mixture of novel compounds (**2.65**) and (**2.69**) (800 mg, 80 %) as a brown liquid.

(**2.65**)

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (app. t, J = 1.6 Hz, 1H, H15), 4.75 (app. s, 1H, H15), 4.54 (dd, *J* = 9.3, 8.3 Hz, 1H, H8), 4.22 (dd, *J* = 9.3, 4.8 Hz, 1H, H8), 4.17 – 4.06 (m, 2H, H12), 3.86- 3.77 (m, 2H, H5/H4), 3.16 (dd, *J* = 11.8, 6.5 Hz, 1H, H4), 2.99 (app. dd, *J* = 14.4, 7.7 Hz, 1H, H7), 2.48 – 2.34 (m, 2H, H6/H9), 2.26 – 2.16 (m, 1H, H9), 1.73 (s, 3H, H16), 1.29 – 1.20 (t, *J* = 7.2 Hz, 3H, H13).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2 (C10), 161.3 (C2), 142.3 (C14), 114.6 (C15), 68.8 (C8), 63.6 (C5), 60.8 (C12), 49.7 (C4), 49.3 (C7), 43.1 (C6), 33.3 (C9), 22.5 (C16), 14.1 (C13).

ν_{max} (FTIR)cm^{-1}: 2980 (C-H), 2913 (C-H), 1748 (C=O), 1726 (C=O), 1263, 1175 (C-O).

HRMS: calcd for $C_{13}H_{19}NO_4Na$, m/z = 276.1206, found 276.1217.

$[\alpha]_D^{23}$ = -14.4 (*c* = 1.01, CH_2Cl_2).

(**2.69**)

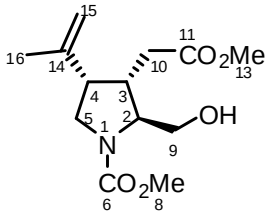
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.89 (app. t, J = 1.5 Hz, 1H, H15), 4.86 (app. s, 1H, H15), 4.52 (dd, *J* = 9.3, 8.3 Hz, 1H, H4), 4.42 (dd, *J* = 9.3, 4.2 Hz, 1H, H4), 4.16-4.09 (m, 2H, H12), 3.82 – 3.73 (m, 1H, H5), 3.47 (app. t, *J* = 10.7 Hz, 1H, H8), 3.40 (app. t, *J* = 10.2 Hz, 1H, H8), 2.78 – 2.67 (m, 1H, H7), 2.57 (dd, *J* = 3.6, 15.7 Hz, 1H, H9), 2.19 (dd, *J* = 9.7, 15.3 Hz, 1H, H9), 2.15 – 2.07 (m, 1H, H6), 1.71 (s, 3H, H16), 1.27 (t, *J* = 7.1 Hz, 3H, H13).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0 (C10), 161.4 (C2), 141.3 (C14), 114.7 (C15), 67.8 (C4), 64.7 (C5), 60.9 (C12), 55.0 (C7), 48.67 (C8), 43.3 (C6), 35.3 (C9), 18.1 (C16), 14.1 (C13).

ν_{max} (FTIR)cm^{-1}: 2974 (C-H), 2904 (C-H), 1750 (C=O), 17129 (C=O), 1206, 1175 (C-O).

HRMS: calcd for $C_{13}H_{19}NO_4Na$, m/z = 276.1206, found 276.1218.

Preparation of methyl (2*S*,3*S*,4*S*)-2-(hydroxymethyl)-4-isopropenyl-3-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (2.64)



(**2.64**)

This known compound was synthesised using a modification of the procedure according to Kern *et al.*[122].

To a stirring solution of ene-product (**2.65**) (500 mg, 1.97 mmol) in MeOH (4 mL) at rt was added in one portion Cs_2CO_3 (32 mg, 0.1 mmol). Following 6 d reaction was quenched with H_2O (5 mL) and extracted with AcOEt (3 x 15 mL). Organics combined, dried (Na_2SO_4) and solvent removed under reduced pressure. The residue was subject to column chromatography eluting with hexanes/ethyl acetate (3:2) to afford the title compound (**2.64**) (426 mg, 80 %) as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.89 (app. s, 1H, H15), 4.64 (app. s, 1H, H15), 3.76 (app. s, 1H, H2), 3.70 (app. s, 5H, H5/H8), 3.65 (s, 3H, H13), 3.47-3.41 (m, 2H, H9), 3.00-2.92 (m, 1H, H4), 2.56 (app. s, br, 1H, H3), 2.29-2.16 (m, 2H, H10), 1.69 (s, 3H, H6).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.7 (C11), 157.3 (C6), 141.6 (C14), 112.9 (C15), 65.8 (C5), 65.4 (C2), 52.8 (C8), 51.7 (C13), 48.3 (C9), 45.6 (C4), 39.0 (C3), 33.0 (C10), 22.3 (C16).

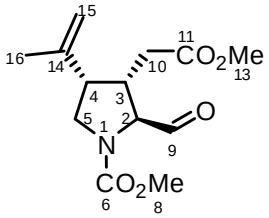
ν_{max} (FTIR)cm^{-1}: 3454 (O-H), 2920 (C-H), 2850 (C-H), 1735 (C=O), 1678 (C=O), 1450, 1376.

HRMS: calcd for $C_{13}H_{22}NO_5$, m/z = 272.11492, found 272.1499.

$[\alpha]_D^{23}$ = -42.3 (*c* = 1.00, CH_3Cl). Lit. $[\alpha]_D^{20}$ = -41.2[55].

R_f = 0.26 (1:1 AcOEt : Petrol).

Preparation of methyl (2*S*,3*S*,4*S*)-2-formyl-4-isopropenyl-3-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (2.63)



(**2.63**)

This novel compound was synthesised using a modification of the procedure according to Parikh *et al.*[123].

Py.SO_3 (3.78 g, 23.7 mmol) was dissolved in DMSO (8.3 mL) and CH_2Cl_2 (11 mL) and cooled to 0°C. Et_3N (4.1 mL, 29.7 mmol) was added dropwise. After 10 min alcohol (**2.64**) (1.61 g 5.93 mmol) in CH_2Cl_2 (11 mL) was added dropwise at 0°C. Mixture was allowed to warm to rt. Following 16 h sat. $NH_4Cl_{(aq)}$ (20 mL) was added and extracted with CH_2Cl_2 (3 x 15 mL). Organics combined, dried (Na_2SO_4) and solvent removed under reduced pressure. The residue was subject to column chromatography eluting with petrol/ethyl acetate (3:1) to afford the title compound (**2.63**) (1.42 g, 89 %) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.58 (s, 0.5H, $H9_{rot}$), 9.55 (s, 0.5H, $H9_{rot}$), 4.90 (app. s, 1H, H15), 4.67 (d, *J* = 13.6 Hz, 1H, H15), 4.19 (d, *J* = 3.1 Hz, 0.5H, $H2_{rot}$), 4.08 (d, *J* = 3.1 Hz, 0.5H, $H2_{rot}$) 3.72 (app. s, 1H, H5), 3.70 – 3.60 (m, 6H, H8/H13), 3.55 (dd, *J* = 10.7, 8.5 Hz, 0.5H, $H5_{rot}$), 3.46 (dd, *J* = 10.1, 8.7 Hz, 0.5H, $H5_{rot}$) 2.91-2.83 (m, 1H, H3), 2.84 – 2.72 (m, 1H, H4), 2.36 – 2.27 (m, 1H, H10), 2.27 – 2.12 (m, 1H, H10), 1.68 (s, 3H, H16).

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.5 (C9), 172.3 (C11), 155.7 (C3), 140.9 (C14), 113.8 (C15), 69.8 (C2), 51.9 (C8), 48.4 (C13), 47.9 (C5), 45.9 (C4), 38.5 (C3), 32.1 (C10), 22.3 (C16).

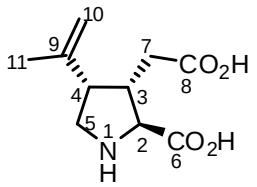
ν_{max} (FTIR)cm^{-1}: 2958 (C-H), 1693 (C=O), 1689 (C=O), 1449, 1380, 1131 (C-O).

HRMS: calcd for $C_{13}H_{19}NO_5Na$, m/z = 292.1155, found 292.1156.

$[\alpha]_D^{23}$ = -58.1 (*c* = 1.05, CH_2Cl_2).

R_f = 0.26 (1:3 AcOEt : Petrol).

Preparation of (-)-α-Kainic Acid (1.1)



(-)-α-kainic acid (**1.1**)

(1) This natural product was synthesised using a modification of the procedures according to Pinnick *et al.*[125] and Oppolzer *et al.*[17].

To a stirring solution of aldehyde (**2.63**) (1.42 g, 5.28 mmol) in ^tBuOH (15 mL) and 2-methyl 2-butene (25 mL) at rt was added dropwise a solution of sodium chlorite (4.30 g, 47.5 mmol) and sodium dihydrogenphosphate (5.76 g, 36.9 mmol) in water (150 mL) over a period of 10 m. After 16 h the volatiles were removed under reduced pressure and the residue was dissolved in water (25 mL) and extracted with hexanes (3 x 25 mL). Aqueous phase was acidified to pH 3 with conc. $HCl_{(aq)}$ and extracted with diethyl ether (3 x 50 mL). Organics combined, dried (Na_2SO_4) and concentrated under reduced pressure to yield a crude acid which was used without further purification.

(2) The crude acid was dissolved in stirring MeOH (70 mL) and NaOH(38%) (70 mL) was added. Mixture heated to reflux. Following 18 h solvent was removed under reduced pressure and crude product was added to a column containing Dowex-50 H^+ (WX8-200 cross-linking, 100-200 wet mesh). Elution with NH_4OH (1M), evaporation and treatment with Amberlite CG-50 (100-200 dry mesh) afforded after recrystallisation from water, the title compound (-)-α-kainic acid (**1.1**) (720 mg, 60 %) as white needle crystals.

^{1}H NMR (500 MHz, D_2O): δ 4.98 (app. s, 1H, H10), 4.69 (app. S, 1H, H10), 4.03 (s 1H, H2), 3.64 (dd, 1H, *J* = 11.5, 8.5 Hz, H5), 3.35 (app. t, *J* = 11.5 Hz, 1H, H5), 3.06-2.99 (m, 1H, H4), 2.98-2.92 (m, 1H, H3), 2.44-2.36 (m, 1H, H7), 2.35-2.27 (m, 1H, H7), 1.70 (s, 3H, H11).

^{13}C NMR (126 MHz, D_2O): δ 176.2 (C8), 173.7 (C6), 139.9 (C9), 113.4 (C10), 65.6 (C2), 46.4 (C5), 45.7 (C3), 40.7 (C4), 33.3 (C7), 22.1 (C11).

v_{max} (FTIR)cm^{-1}: 3534, 2976 (C-H), 2528 (C-H), 1689 (C=O), 1615 (C=O), 1383, 1276, 891.

HRMS: calcd for $C_{10}H_{16}NO_4Na$, m/z = 214.1074, found 214.1077.

$[\alpha]_D^{23}$ = -14.6 (*c* = 0.65, H_2O). Lit. $[\alpha]_D^{20}$ = -14.6[66].

Mp. 244.5-245°C. Lit Mp. 245°C[66]

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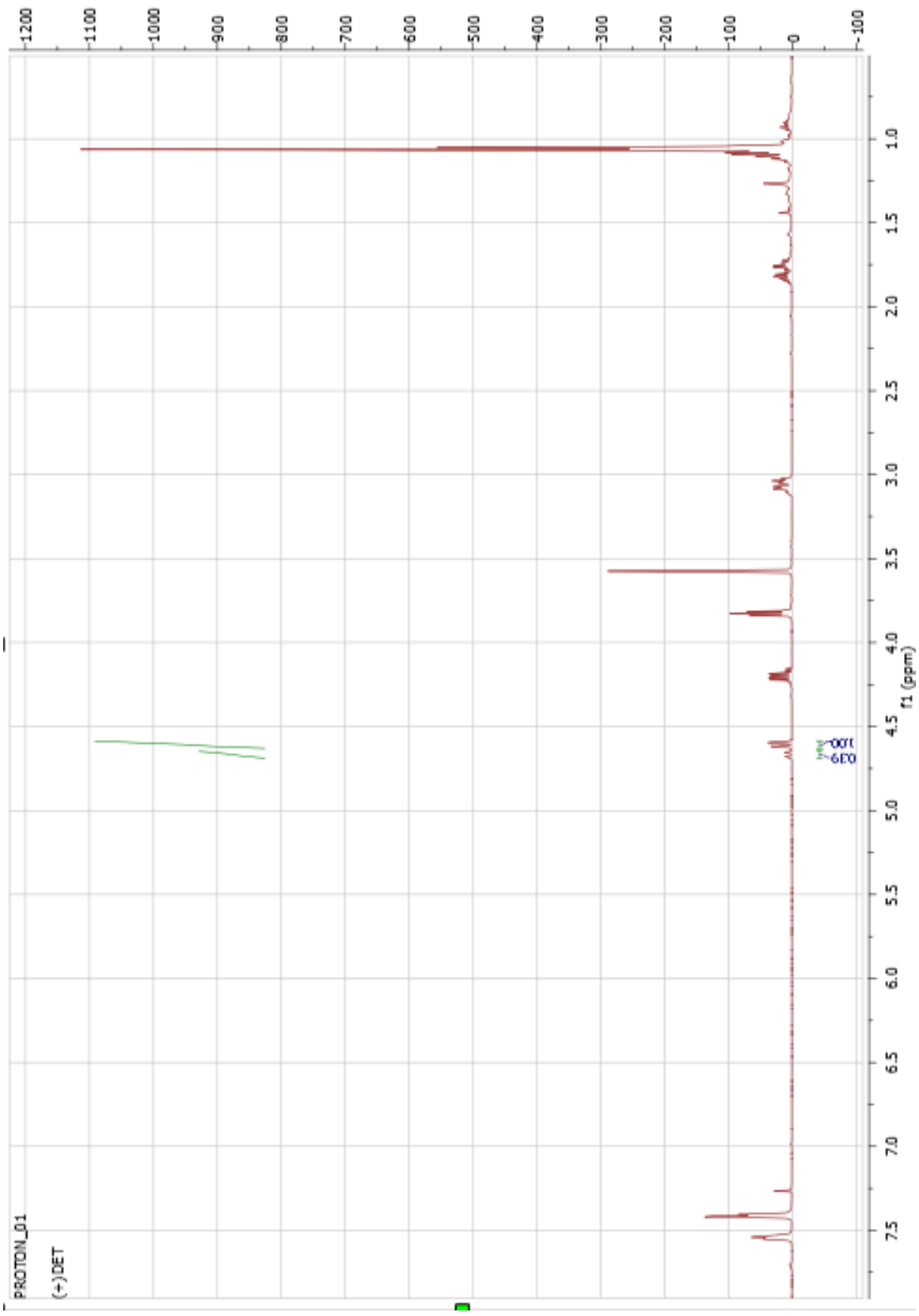
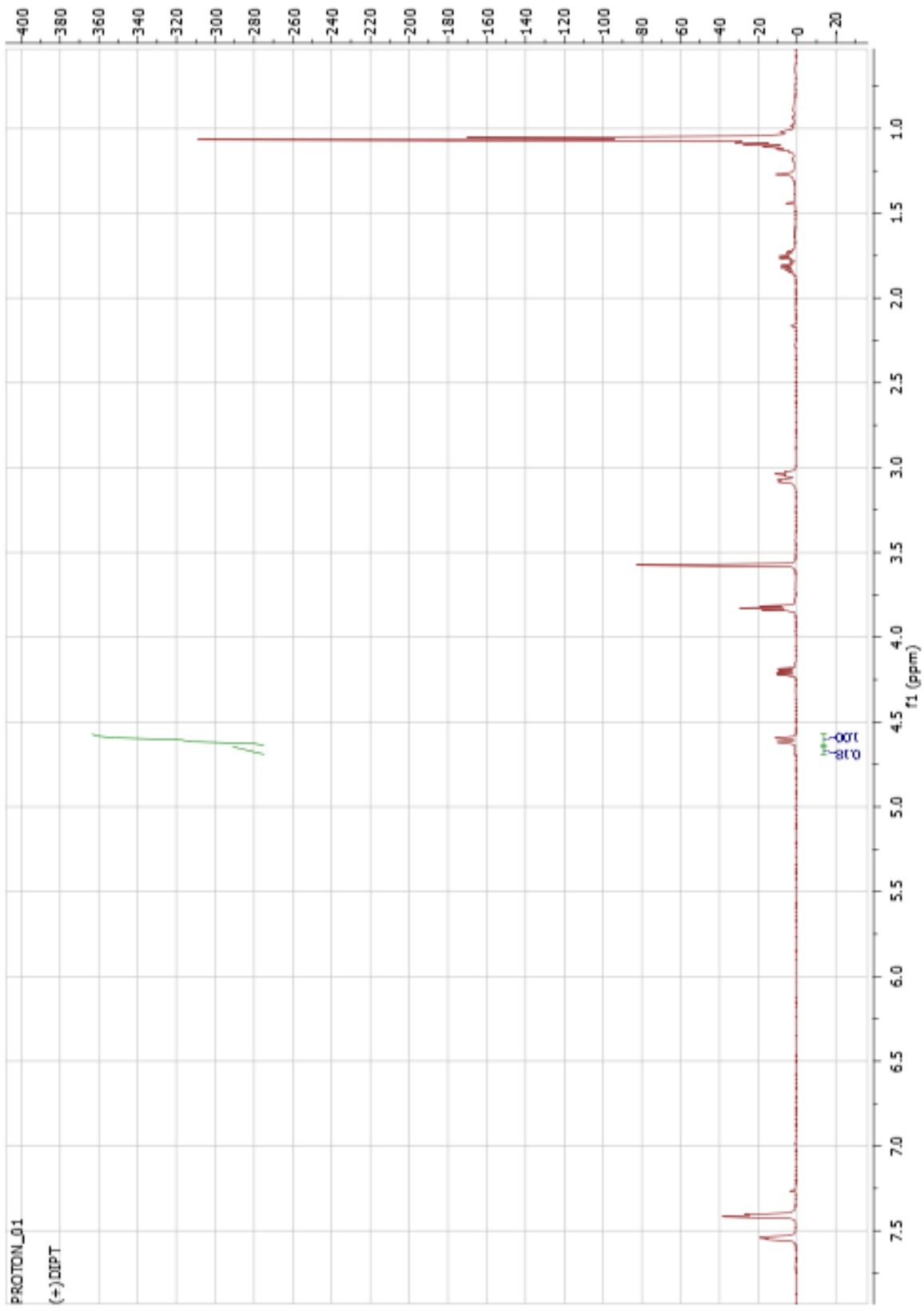
APPENDICES

^{1}H-NMR Spectra for Moshers ester of (2.37) epoxidised with (+)DET

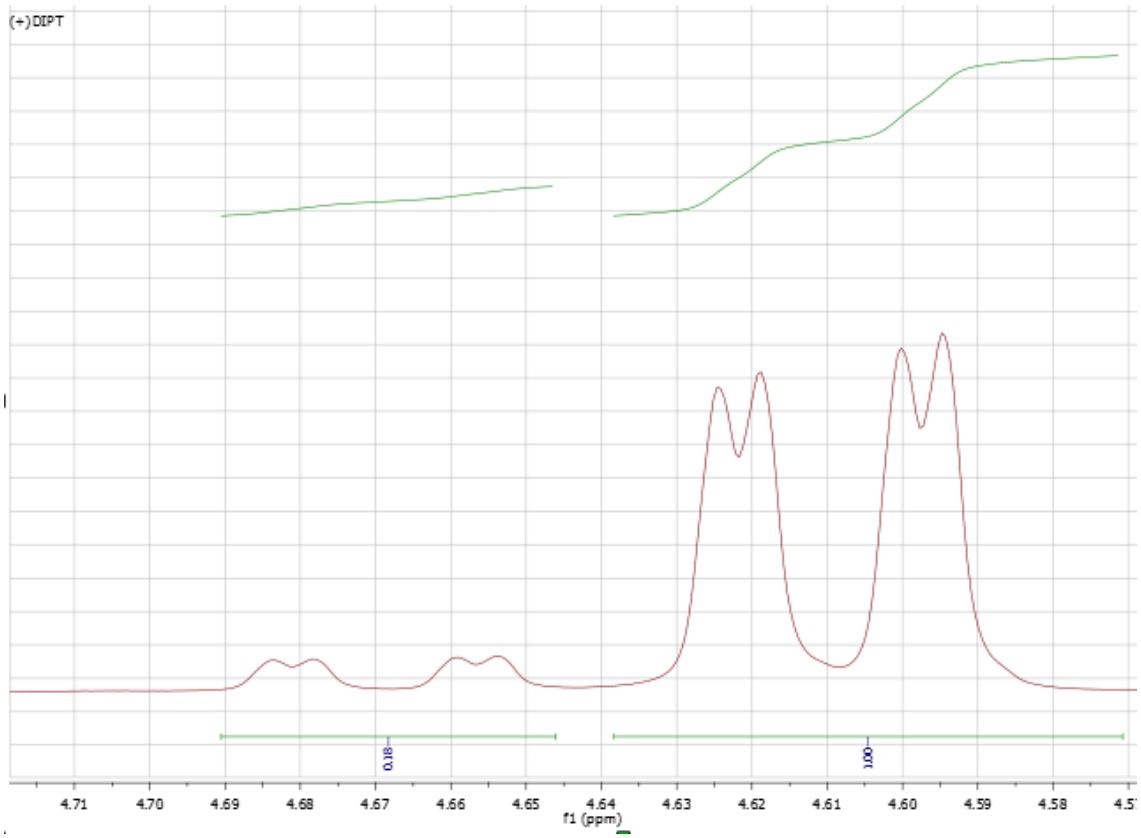


^{1}H-NMR Spectra for Moshers ester of (2.37) epoxidised with (+)DIPT



Zoom view of dds around δ 4.64 (+)DET

Zoom view of dds around δ 4.64 (+)DIPT



Crystallographic Information for (-)-(α)-kainic acid (1.1)

Table 1. Crystal data and structure refinement for $C_{10}H_{15}NO_4 \cdot H_2O$ (Kainic Acid – monohydrate)

Identification code	jun511	
Empirical formula	C10 H17 N O5	
Formula weight	231.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P* 2_1 (No.4)	
Unit cell dimensions	a = 8.1222(4) Å	α= 90°.
	b = 5.8322(3) Å	β= 94.629(2)°.
	c = 11.9013(6) Å	γ = 90°.
Volume	561.93(5) $Å^3$	
Z	2	
Density (calculated)	1.37 Mg/m^3	
Absorption coefficient	0.110 mm^{-1}	
F(000)	248	
Crystal size	0.22 x 0.20 x 0.15 mm^3	
Theta range for data collection	1.72 to 27.50°.	
Index ranges	-10<=h<=10, -7<=k<=7, -15<=l<=15	
Reflections collected	7320	
Independent reflections	1400 [R(int) = 0.060]	
Completeness to theta = 27.50°	98.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1400 / 1 / 165	
Goodness-of-fit on F^2	1.165	
Final R indices [I>2sigma(I)]	R1 = 0.041, wR2 = 0.122	
R indices (all data)	R1 = 0.052, wR2 = 0.139	
Largest diff. peak and hole	0.48 and -0.29 e.$Å^{-3}$	

Hydrogen atoms on CO_2H, NH_2 and water located on a difference map and refined; all others in calculated positions. Extensive hydrogen-bonding present in the crystal structure

Absolute stereochemistry not determined

Data collection KappaCCD , Program package WinGX , Abs correction not applied

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for jun511. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-1988(2)	2349(4)	6594(2)	31(1)
O(2)	-411(3)	4139(4)	5421(2)	27(1)
O(3)	3102(3)	8914(4)	5927(2)	24(1)
O(4)	5568(2)	7193(4)	6029(2)	28(1)
O(5)	8482(4)	7722(6)	7479(2)	39(1)
N	4467(3)	3082(5)	6504(2)	18(1)
C(1)	4621(3)	2847(6)	7776(2)	23(1)
C(2)	3455(3)	4682(5)	8185(2)	20(1)
C(3)	2103(3)	4895(5)	7193(2)	18(1)
C(4)	3181(3)	4860(5)	6184(2)	17(1)
C(5)	2821(4)	4264(6)	9330(2)	24(1)
C(6)	3272(4)	2497(7)	9977(3)	33(1)
C(7)	1675(5)	6088(7)	9702(3)	37(1)
C(8)	851(3)	2917(5)	7193(2)	21(1)
C(9)	-656(3)	3143(5)	6382(2)	21(1)
C(10)	4043(3)	7175(5)	6036(2)	18(1)

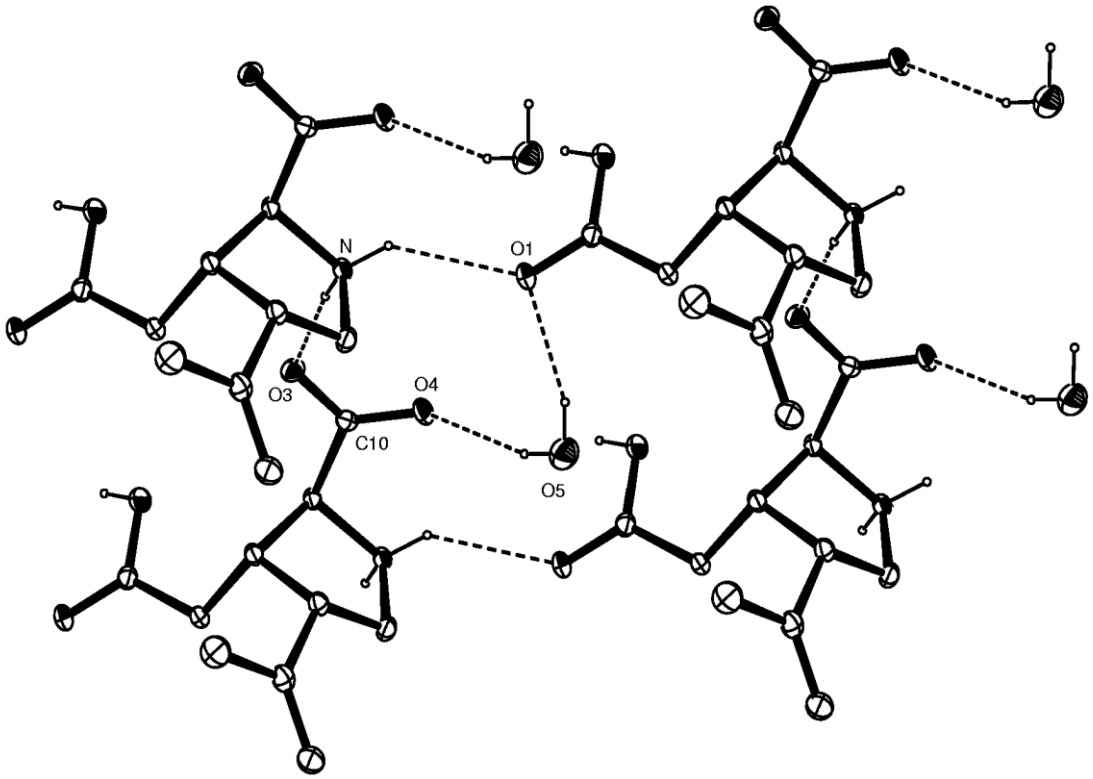
Table 3. Bond lengths [Å] and angles [°] for jun511.

O(1)-C(9)	1.222(3)
O(2)-C(9)	1.312(4)
O(3)-C(10)	1.270(4)
O(4)-C(10)	1.240(3)
N-C(4)	1.499(4)
N-C(1)	1.516(4)
C(1)-C(2)	1.534(4)
C(2)-C(5)	1.515(4)
C(2)-C(3)	1.551(4)
C(3)-C(8)	1.538(4)
C(3)-C(4)	1.542(3)
C(4)-C(10)	1.538(4)
C(5)-C(6)	1.320(5)
C(5)-C(7)	1.503(5)

C(8)-C(9)	1.502(4)
C(4)-N-C(1)	108.4(2)
N-C(1)-C(2)	104.5(2)
C(5)-C(2)-C(1)	115.9(3)
C(5)-C(2)-C(3)	115.2(2)
C(1)-C(2)-C(3)	103.4(2)
C(8)-C(3)-C(4)	114.0(2)
C(8)-C(3)-C(2)	111.6(2)
C(4)-C(3)-C(2)	100.4(2)
N-C(4)-C(10)	108.8(2)
N-C(4)-C(3)	103.9(2)
C(10)-C(4)-C(3)	111.7(2)
C(6)-C(5)-C(7)	122.0(3)
C(6)-C(5)-C(2)	123.4(3)
C(7)-C(5)-C(2)	114.5(3)
C(9)-C(8)-C(3)	116.1(2)
O(1)-C(9)-O(2)	123.2(3)
O(1)-C(9)-C(8)	121.6(3)
O(2)-C(9)-C(8)	115.2(2)
O(4)-C(10)-O(3)	125.9(3)
O(4)-C(10)-C(4)	118.2(3)
O(3)-C(10)-C(4)	115.9(2)

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O2-H2X	0.835	1.805	160.81	2.608	O3 [-x, y-1/2, -z+1]
O5-H5Y	0.809	2.057	160.44	2.831	O4
O5-H5X	0.864	2.084	160.14	2.911	O1 [x+1, y+1, z]
N -H2N	0.887	1.859	169.52	2.736	O3 [x, y-1, z]
N -H1N	0.810	2.221	112.16	2.636	O4
N -H1N	0.810	2.229	141.09	2.904	O1 [x+1, y, z]


N
O1
O3
O4
C10
O5